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Report of the Special Advisory Committee on Carcinogens

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Report of the Special Advisory Committee on Carcinogens

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Report of the Special Advisory Committee on Carcinogens

1. INTRODUCTION

The suggestion that substances in the workplace might cause cancer was first made by Percival Pott in 1775 on the basis of his experience with scrotal cancer in chimney sweeps. The substances which were identified as causing cancer in these early chimney sweeps are still being inhaled by individuals such as coke oven workers, some of whom are dying of lung cancer at a rate 10 times higher than other steel workers.

In the past, the effects of carcinogenic substances have been deduced by observing that cohorts of individuals exposed to a substance show an increased incidence of cancer. It is now well established that chemical substances can cause cancer, and it is possible to predict, with reasonable reliability, by means of appropriate tests, the potential of a substance to be a carcinogen.

The first part of this report sets forth some general facts about cancer and about cancer deaths in Ontario. The second part consists of summaries of four 'case histories'*, which illustrate what is known about carcinogens and environmental and lifestyle factors that can cause cancer. The report then looks at the overall cancer burden in Ontario and gives consideration to strategies and methods for screening new substances.

2. THE BIOLOGY OF CANCER

Simply put, cancers arise when cells lose their 'social inhibitions'. These altered cells fail to recognize the signals that regulate their normal functions, growth and location in the organism. As a result, these cells proliferate to form tumour masses. When they keep within their normal territory and do not invade the surrounding tissues, they form 'benign' tumours. If the abnormal cells spread into neighbouring tissues or to distant regions by way of the circulation, they are termed 'malignant' tumours or cancers.

Cancers are classified according to cell type: the carcinomas arise from the sheets of cells covering the exterior and interior (e.g. mouth) surfaces of the body and lining the various glands i.e. epithelial cells; sarcomas arise in supporting tissues (such as bone cells, blood vessels and muscle). Leukemias and lymphomas involve abnormal proliferation of blood cells or their precursors. More than 90 per cent of human cancers arise in epithelial cells, mainly in the surface epithelia such as the skin, airways and digestive tract, which are in direct contact with the substances of the outside world.

*-the complete texts are to be found in Appendices A-D.

The transformation of normal cells to malignant cancer cells is a complex, multi-step process which is still not well understood. It is clear, however, that carcinogenic chemicals, ionizing and UV radiation can increase the rate at which some of the steps take place and thus greatly increase the probability of a tumour appearing in an exposed individual.

Study of the causes of cancer is complicated by the fact that there is a period of 5-40 years between initial exposure to the agent(s) that causes cancer and the clinical appearance of tumours.

The evolution of a normal cell into a tumour cell begins with an event referred to as 'initiation', which is generally believed to involve damage to chromosomal DNA by the carcinogen (or by a reactive derivative formed from the carcinogen by metabolic processes within the body). The consequence of such damage may be gene mutation, chromosomal rearrangements or alterations in cellular control mechanisms which accomplish one of the steps required in the development of malignancy. Compounds such as benzo(a)pyrene, vinyl chloride, β -naphthylamine and agents such as UV light and ionizing radiation are considered to be 'initiators'. With most initiators, large or repeated doses suffice to cause tumours without the need for additional stimuli. Other compounds such as catechol, pyrogallol, pyrene and benzo(e)pyrene, which do not themselves initiate cancers, may increase the potency of initiating carcinogens *if present simultaneously*. Such compounds are called 'co-carcinogens'.

Initiated cells are not yet malignant, and other events are required before malignancy is manifested. While detailed knowledge of these important events is scanty, it is established that chemicals can also influence the rate at which these events take place. One well-studied (but poorly understood) phenomenon is that of 'promotion' in which a compound which does not 'initiate' tumour development can greatly increase the rate of evolution of cells which have previously been 'initiated' with such low doses of carcinogens that few, if any, tumours would have been induced by the initiator alone. Promoters can exert their influence even when applied long after the initiation event. The classical example of a tumour-promoting substance is croton oil—a highly irritating plant material. However, in experimental animals, other substances, including phenol, anthralin and n-dodecane, are promoters for skin tumours and saccharin is probably a promoter for bladder tumours. Various mechanisms have been suggested to account for promotion. These include stimulation of cell division, membrane changes, and induction of enzymes, but again, the specific mechanisms have not been established.

It seems probable that exposure of humans to environmental (including occupational) or 'life style' initiators will cause initiation events in some cells. In the absence of promoters, these cells may remain quiescent, whereas in the presence of promoters, they may have a much higher probability of developing into malignant tumours. Thus, from the point of view of cancer prevention, it may be as important to minimize the exposure of humans to promoters as to minimize exposure to initiators.

While a later section of this report deals in detail with assay systems for carcinogens, it is worth noting that there are now reasonably useful routine assay systems for the detection of initiators, but that assays for the detection of promoters are in a much more primitive state.

Lessons

1. The development of cancer involves many steps; interfering successfully with any of these could prevent the onset of malignant disease.
2. Environmental or lifestyle initiators of cancer need attention, but so do promoters.

3. SUMMARIES OF CASE HISTORIES

Following are summaries of the four 'case histories' referred to in the introduction. The purpose of these case histories is to provide examples of universally recognized carcinogens and to identify the cancers which they are known to produce, with particular reference to how the carcinogens were eventually identified. The examples are chosen for the clarity of the evidence, not because they specifically identify lifestyle or environmental factors.

1. Ionizing Radiation

The early workers with ionizing radiation were unaware of its carcinogenic properties, and many of those early workers, including some famous scientists working with radiation, succumbed to its effects because of lack of protection.

Ionizing radiations include X- and gamma-rays, electrons, alpha particles and neutrons.

Radiation hazards have been under scrutiny for over 80 years. The chief sources of human data are the populations exposed to whole-body irradiation at Hiroshima and Nagasaki, patients exposed to radiation therapy, and various occupationally-exposed populations such as uranium miners and radium-dial painters. A clear-cut increase in cancer incidence and mortality with increasing dose of ionizing radiation has been demonstrated for many types of cancer in human populations as well as in laboratory animals. The non-threshold concept, which is clearly demonstrated for ionizing radiation, indicates that some degree of risk is associated with any exposure to ionizing radiation. Awareness of the long-term effects of radiation exposure led to development of the 'maximum permissible exposure' concept. Attempts have been made to relate this allowable exposure to the natural ionizing radiation in our environment as a basis for defining a natural level of risk.

There are several natural sources of radiation exposure, including terrestrial radiation, cosmic radiation and radiation from radioactive elements in our bodies. Medical applications of radiation, particularly X-rays, are a further source of exposure. Occupational exposures may exceed background radiation by several fold. Occupational exposure to ionizing radiation became of significance only following the discoveries of X-rays in 1895 and radioactivity in 1896. The fact that it can damage living tissue became apparent

very quickly. Radiation injuries suffered by luminous watch-dial painters who had inhaled or swallowed radium, were first reported in 1925. At high levels of exposure, acute destruction of bone and bone marrow resulted in death within a few years. The experience of early workers also revealed that repeated doses of radiation that are too small to produce any immediate reaction, may produce cancer many years later.

Types of Cancers Induced

Cancers induced by ionizing radiation are indistinguishable from those occurring naturally, hence their existence can be inferred only on the basis of a statistical excess above natural incidence. Cancer may be induced by ionizing radiation in nearly all the tissues of the human body, although tissues and organs vary considerably in their sensitivity. The types of cancer which show the highest sensitivity to radiation induction are leukemia and breast cancer.

Latent Period

Because of the very long latent periods which may separate exposure to radiation and the development of effects in humans, the true health risk of radiation exposure can be assessed only with extremely long follow-up (30 years or more) of the populations under study.

Effect of Age

Age at exposure to ionizing radiation has an important influence on its carcinogenic effect. For example, the excess risk of breast cancer appears to be highest for women exposed in the second decade of life, when major hormonal changes are taking place. An association between prenatal exposure to ionizing radiation and an increased risk of developing malignancy during childhood has been established, but there remains some question about the extent to which this represents a casual relationship.

Other Variables

Various host or environmental factors may act together with radiation to affect cancer incidence. For example, a cigarette smoker appears to be at greater risk of developing lung cancer from radiation exposure than is a non-smoker.

Current evidence would seem to be against large differences in sensitivity to ionizing radiation within the population.

The carcinogenic effects of ionizing radiation comply with the criteria of causation of Bradford Hill¹. (See page 173). For example, the association of exposure to ionizing radiation and subsequent deaths from leukemia is strong and consistent (relative risk greater than 20 in the Hiroshima and Nagasaki atomic bomb survivors exposed to 400 rads or more). The strong association is limited to particular sites and types of disease (all forms of leukemia, except chronic lymphocytic leukemia, were increased in incidence in atomic bomb survivors). The temporal relationship, existence of a biological gradient, biological plausibility and coherence criteria are all met.

Lesson

The history of ionizing radiation is a classic example of recognition of the importance of carcinogenic effects only after the exposure of human populations. This, however, has led to considerable efforts being made to reduce the risk of exposure to ionizing radiation; an example is the radiation control program of the nuclear power industry in Ontario.

2. Vinyl Chloride

Vinyl chloride exposure in the workplace was first recognized as cancer-inducing in 1974 in a branch of a chemical company. This recognition was made because of the occurrence of a small cluster of cases of an unusual form of cancer, a rare liver cancer called angiosarcoma. Only then did scientists appreciate the significance of the finding of a similar cancer, a few years before, in experimental rats exposed to vinyl chloride. Since then, this same type of liver cancer has been reported in workers exposed to vinyl chloride in several countries, including Canada, where it has been reported in Ontario and Quebec.

This 'case study' illustrates the possible value of screening for carcinogens in experimental animals. If action had been taken as soon as the experimental findings had been reported, some workers might have been prevented from developing this form of liver cancer.

Angiosarcomas associated with exposure to vinyl chloride probably take from 15 to 25 years to develop. However, the exposure to the chemical need not be over the whole latency period. Several workers developed cancer 20 or 30 years after a relatively brief but intense exposure (5 months to 3 years). This emphasizes the need for minimizing or, if possible, avoiding completely any exposure to vinyl chloride. Although exposure levels of less than 10 parts per million were considered in the mid 1970s to be difficult to achieve, levels of 0.5 ppm or even less are now routinely maintained in Sweden and the USA. In the USA, production dropped by 25 per cent during the year that stringent controls were put into place. However, production the following year (1975) increased by 37 per cent, thus not only making up for the loss, but exceeding the usual annual increase of around five/six per cent.

As with some other carcinogens, vinyl chloride itself is not cancer producing, but must first be converted by the metabolic processes in the body, especially the liver, to an active derivative. It is this chemically reactive product that damages the liver cells in such a manner as to start the reaction that results ultimately in liver cancer. Although histological changes can be seen in the liver during this long period of development, they are generally not severe enough to be picked up on examination of the worker, nor are blood tests indicative of early changes. It is so far not possible to predict which exposed individuals may be susceptible to cancer induction with vinyl chloride.

We do not have any data on how much exposure is needed to induce liver cancer. It is assumed by many scientists that no threshold level exists for vinyl chloride. This is considered to be the case for all carcinogenic substances.

So far, only angiosarcoma and the more common type of liver cancer, liver cell cancer, have been shown in humans to be associated with human exposure to vinyl chloride. However, in experimental animals, vinyl chloride is also associated with an increased incidence of several other types of cancers. The possibility that vinyl chloride can induce other forms of human cancer should be considered in view of the similarities between the disease patterns in people and in experimental animals exposed to carcinogens. It is to be hoped that no vinyl chloride-induced cancer will occur in those who began working in factories with the new tight controls on exposure established in the last few years. However, we may, unfortunately, continue for another 20 or more years, to see workers who were exposed prior to 1975 or 1976 develop vinyl chloride-associated disease because of the latency period between exposure to a carcinogen and the development of cancer.

Lessons

1. Animal screening would have detected the carcinogenic effects of vinyl chloride.
2. Because vinyl chloride produced a very rare form of cancer, its effect was easy to detect in humans.
3. Once the problem was recognized, it was possible for industry to introduce control measures that resulted in very low levels of exposure to vinyl chloride.

3. Smoking

In this section, we are using smoking data as an example of a carcinogen largely influenced by lifestyle, for which the effects on humans have been well documented.

Smoking can interact with factors in the workplace environment to increase greatly the risk of developing lung cancer. For example, the risk of lung cancer in a person who smokes heavily is almost 11 times greater than in a non-smoker. The risk of an asbestos worker developing lung cancer is about five times greater than that of a person who is not exposed to the substance, while the risk of developing lung cancer when asbestos exposure is combined with cigarette smoking is 53 to one.

Lung Cancer

In Canada, lung cancer is the most important* cancer in men and is rapidly approaching this position in women. There is a continued upward trend in overall mortality rates from lung cancer. However, there is now some indication of a downturn in mortality in males in the 40 to 49 age cohort, which has also shown a decreased incidence of smoking. In females there is no indication of any slowdown in the rate of increase, and the incidence of smoking among females continues to increase.

*-i.e. showing high mortality because of high incidence, together with a very low cure rate.

There are substantial variations in incidence and mortality internationally, though nearly all countries have seen increases in the rates of disease, some for several years. The marked international variation confirms the importance of environmental and lifestyle factors, as do the changes that occurred in the rates of disease in groups of migrants. For example, those who migrated from Britain to Canada, Australia and South Africa tended to end up with rates intermediate between those they might have been expected to have experienced if they had remained in Britain and those that prevailed in the host country.

The increases that were seen in mortality in every country appeared to follow the increase in tobacco usage, particularly cigarette consumption, after an appropriate latent interval. Several long-term studies confirmed the increased risk of death from lung cancer with use of any form of tobacco, but most specifically, usage of cigarettes. There is a strong dose-response relationship for different cigarette consumption categories. Although the suggestion was first made in the 1930s that the increase in lung cancer rates in men was due to cigarette smoking, studies did not substantiate this until the 1950s, and even then, the association was not generally accepted as causal until the 1960s. The incidence of lung cancer in smokers appears to be unrelated to age, the latency period being the same regardless of the age at which smoking commenced. Studies indicate that the lower lung cancer rate in women is only a reflection of lower smoking levels overall, not a difference in biological susceptibility to the carcinogens in tobacco. Currently, in Canada, cigarette smoking is estimated to account for approximately 80 per cent of the lung cancer in males and nearly 60 per cent in females.

Those who stop smoking appear to have acquired a certain degree of risk at the time they stop and this degree of risk persists, though in comparison with those who continue to smoke, it becomes less with time.

Other forms of cancer related to smoking are: bladder cancer, laryngeal cancer, oral and pharyngeal cancer and gastro-intestinal cancer.

Conclusion

Smoking of cigarettes and other tobacco products is carcinogenic in humans, complying with most of Bradford Hill's criteria of causation. Thus, the association is strong (relative risk 10+ for lung cancer); it is consistent in many studies and countries using different methodologies; the temporality of the association is correct; there is a marked biological gradient or dose response curve, with no evidence of a threshold of effect; it is plausible, consistent with biological knowledge, and is coherent, i.e. does not conflict with the known facts of biology and natural history of cancer. It is, of course, not specific in the sense that many different types of cancers and some non-cancerous diseases are caused by cigarette smoking, though perhaps this is not surprising in view of the multitude of different substances in tobacco likely to be involved. Further, evidence from studies in humans has been hard to come by, though many regard the effect of cessation of cigarette smoking with reduced risk of most smoking-induced cancers, subsequently, as at least partly complying with this criterion.

For lung cancer, cigarette smoking is synergistic with exposure to asbestos and other carcinogens. Similar effects have not been confirmed for other types of cancer, though this possibility should be borne in mind. Currently, in Canada, the average life expectancy of cigarette smoking males is seven years less than that of non-smokers. The lifetime risk of death from cigarette-associated cancers in males (after correcting for other causes of death) approximates to 15 per cent compared to the less than three per cent risk of death from these cancers for non-smokers. Most of this difference is due to lung cancer (12 per cent compared to less than two per cent). Hence, strong endeavours are being made to reduce cigarette smoking, and to attempt to develop cigarettes that are less carcinogenic.

Lesson

The studies of smoking represent one of the best examples of careful epidemiological work showing the close association between a major source of carcinogens and cancer, and the relative failure of public attitude and policy to do anything about it.

4. β -Naphthylamine

A variety of synthetic dyes was introduced into commerce during the latter part of the 19th century. Many, including β -naphthylamine, were based on aromatic amines, which turned out to be powerful carcinogens and induced bladder tumours in hundreds of workers before the situation was brought under control. A salt paste produced in the process was dried on trays and powdered in open mills, thus exposing the workmen to the dusts. With a change in the processing technique, more workers were exposed to the hazard as β -naphthylamine vapour was carried throughout the plant.

β -naphthylamine was first manufactured on a large scale in 1889. During the last decades of the 19th century, large dye works developed in Germany and Switzerland. By 1913, over a hundred cases of occupational bladder cancer were known, and the German chemical industry introduced protective measures. With the outbreak of the First World War, the Allied Countries, cut off from German supplies, began to develop their own industries, and the German and Swiss experience in identifying the hazards of β -naphthylamine production was ignored. Despite an ever-increasing number of cases, no concerted effort was made in Britain to address the problem until after the Second World War.

In 1954, the 'Case' study of bladder cancer in the British chemical industry showed that 10 per cent of the occupational group studied had developed bladder cancer. These workers had been engaged in the manufacture or use of benzidine, β -naphthylamine and α -naphthylamine. It was shown that the risk of one of these workers developing bladder cancer from exposure to β -naphthylamine was 61 times that of a man in the general population. Moreover, the occupational bladder cases occurred at much younger ages than in the general population. The age at onset of bladder cancer was directly related to the age of entry into the occupation. There was much variation in the latent period, the average time of onset being about 18 years after first exposure. Further studies showed that as the dose increased, the percentage of the individuals affected also increased and the latent period was shortened.

There are now data to show that β -naphthylamine is carcinogenic in some animal species. However, it is not β -naphthylamine itself which initiates the process of tumour induction, but a metabolite formed in the liver and excreted in the urine.

The presence, use and manufacture of β -naphthylamine in factories is prohibited in the UK, and its use is regulated in the US. In Ontario, β -naphthylamine is regarded as a known carcinogen to which no exposure should be permitted. In general, it has been possible to substitute non-carcinogenic materials for β -naphthylamine and to avoid its use as a synthetic intermediate.

While pure as well as commercial β -naphthylamine and benzidine induce tumours, α -naphthylamine is a very much less potent carcinogen and there is no convincing evidence that pure α -naphthylamine is a hazard. The industrial hazard which had earlier been associated with the use of commercial α -naphthylamine was, in fact, a consequence of contamination by the β -isomer.

Lesson

This is an example of the failure of industry in one country to take into account evidence developed in another country.

4. CANCER TRENDS IN ONTARIO

One widely-held belief is that the increased use of chemicals and other changes in lifestyle have led to an increase in incidence of cancer. In this chapter we examine the actual evidence² of the problems in Ontario. Figures 1-4 on page 153 give an indication of trends in recent years.

Cancer was the underlying cause of death for 13,584 Ontario residents in 1978. It accounted for 22.4 per cent of all deaths in Ontario and was the second leading cause of death in both males and females. (Accidents were the leading cause of death in the young (under 34) and circulatory disease exceeded cancer in those over the age of 35). Cancer was the leading cause of death in women between the ages of 35 and 59, accounting for 44.9 per cent of the deaths in this category. The majority of deaths from cancer in both sexes occurred over the age of 55.

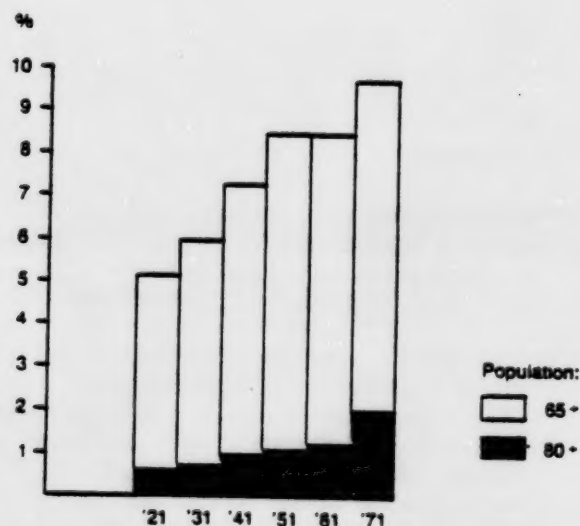
In men, cancer of the lung accounted for the largest proportion of cancer deaths, followed by cancer of the large intestine and prostate. In women, cancer of the breast and large intestine were responsible for the largest proportion of cancer deaths, followed by cancer of the lung and ovary.

Between 1950 and 1977, the age-adjusted cancer mortality rates for males increased, whereas in females mortality rates declined.

Mortality figures for individual sites of cancer have varied. For both sexes, deaths from lung cancer increased at all ages, a change which can be primarily attributed to smoking. The mortality rate from cancer of the lung in females was below that of males. However, in recent years, the rate of increase in the female mortality rate from cancer of the lung has exceeded that of males. In males, mortality from cancer of the stomach declined.

There was no change in mortality from cancer of the bladder, prostate or intestine. In females, mortality rates from cancer of the breast, intestine and ovary showed no change, whereas there was a general decline in mortality from cancer of the cervix and uterus.

The incidence of cancer increases steadily and dramatically with age—males over 80 suffering over one hundred times the death rate from cancer of males under 30. As a result of this strong age effect, the total incidence of cancer in a population will depend to a large extent on the age distribution of the population. Thus, during the first years of this century, life expectancy was limited since many people died of infectious diseases at relatively young ages. The fact that many more people now live longer means that a greater percentage of the population will now die of cancer. The following figure shows the elderly as a percentage of the total population of Canada between the years 1921 and 1971:



Because of the growth of the population in the past few decades, the total number of cancer deaths has also increased. The strong age dependence also means that one cannot usefully compare the incidence of (or mortality from) cancer in different populations unless these have the same proportion of the different age groups. Since this is, in general, not the situation, epidemiologists have devised means of 'age-adjusting' the data. This process involves using the data for each age group (e.g. 40-44, 45-49, etc.) in real populations to compute the 'age adjusted' frequency in a hypothetical reference population. By this means, the cancer experience in different geographical areas, occupational groups and the like can be compared in a meaningful way.

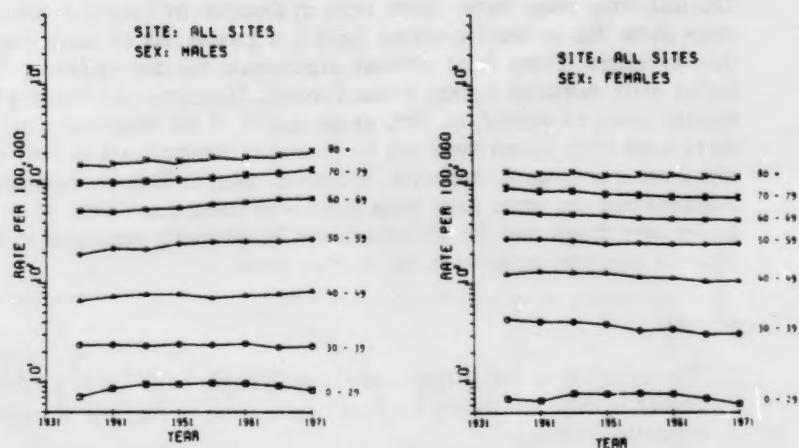


Fig 1. Age group-specific mortality rates for all sites of cancer by sex, 1934-1973.

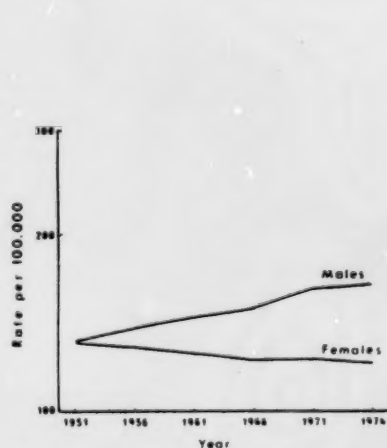


Fig. 2 Age-adjusted mortality rates for all cancer sites by sex, Ontario, 1950-1977. (Age adjusted to the 1961 population of Ontario)

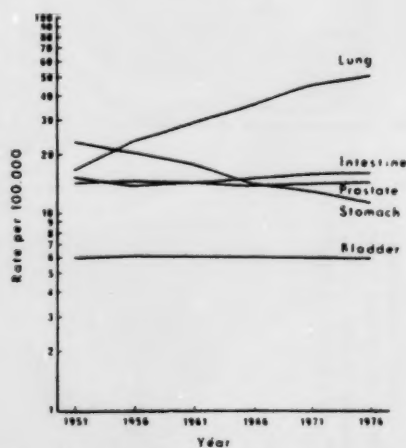


Fig. 3 Age-adjusted mortality rates for selected male cancer sites, Ontario 1950-1977. (Age adjusted to the 1961 male population of Ontario)

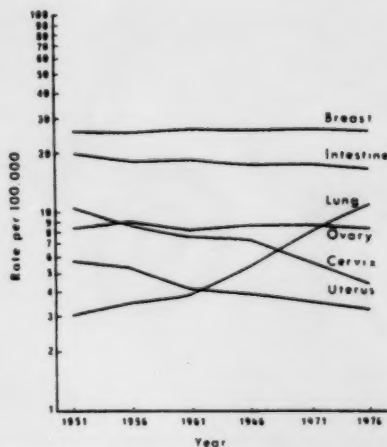
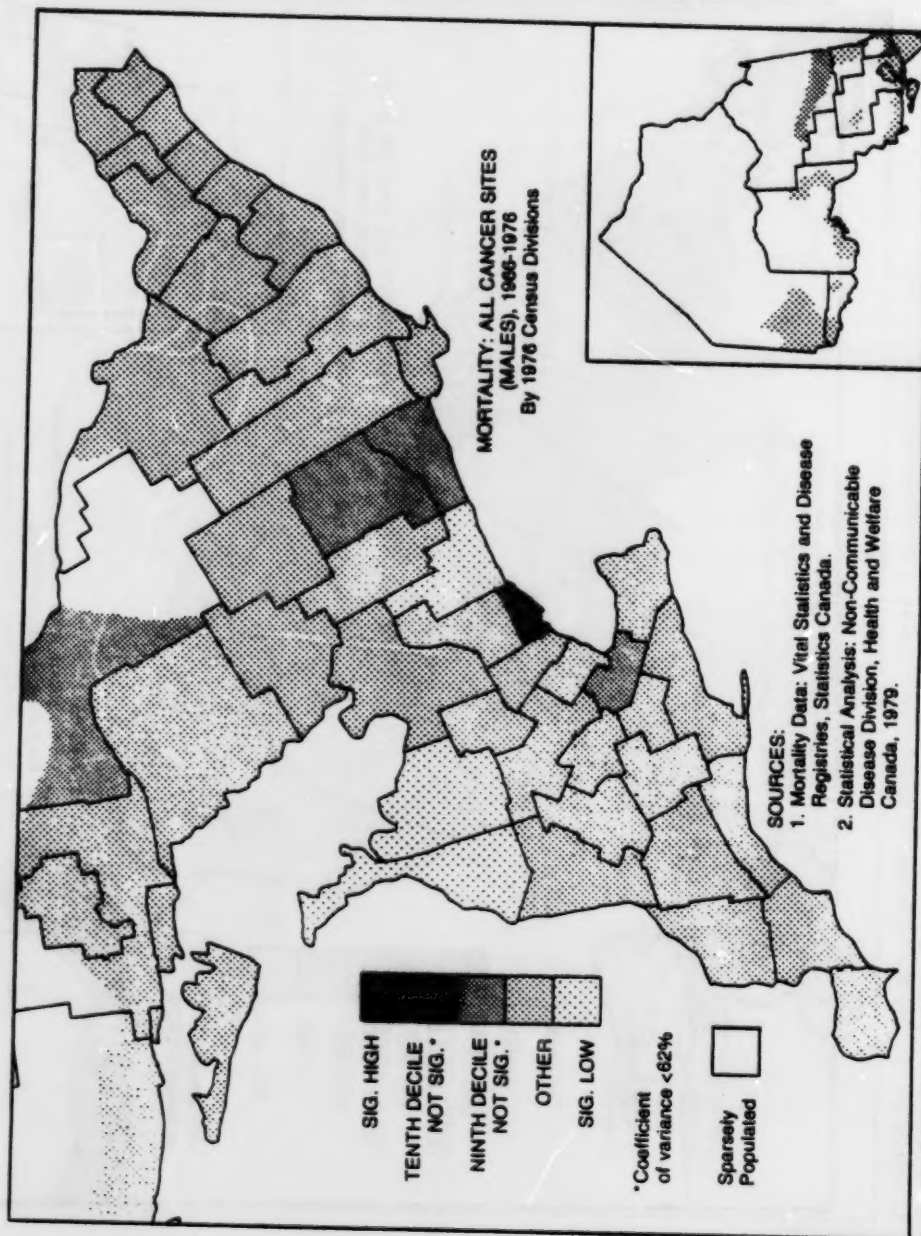


Fig. 4 Age-adjusted mortality rates for selected female cancer sites, Ontario, 1950-1977. (Age adjusted to the 1961 female population of Ontario)

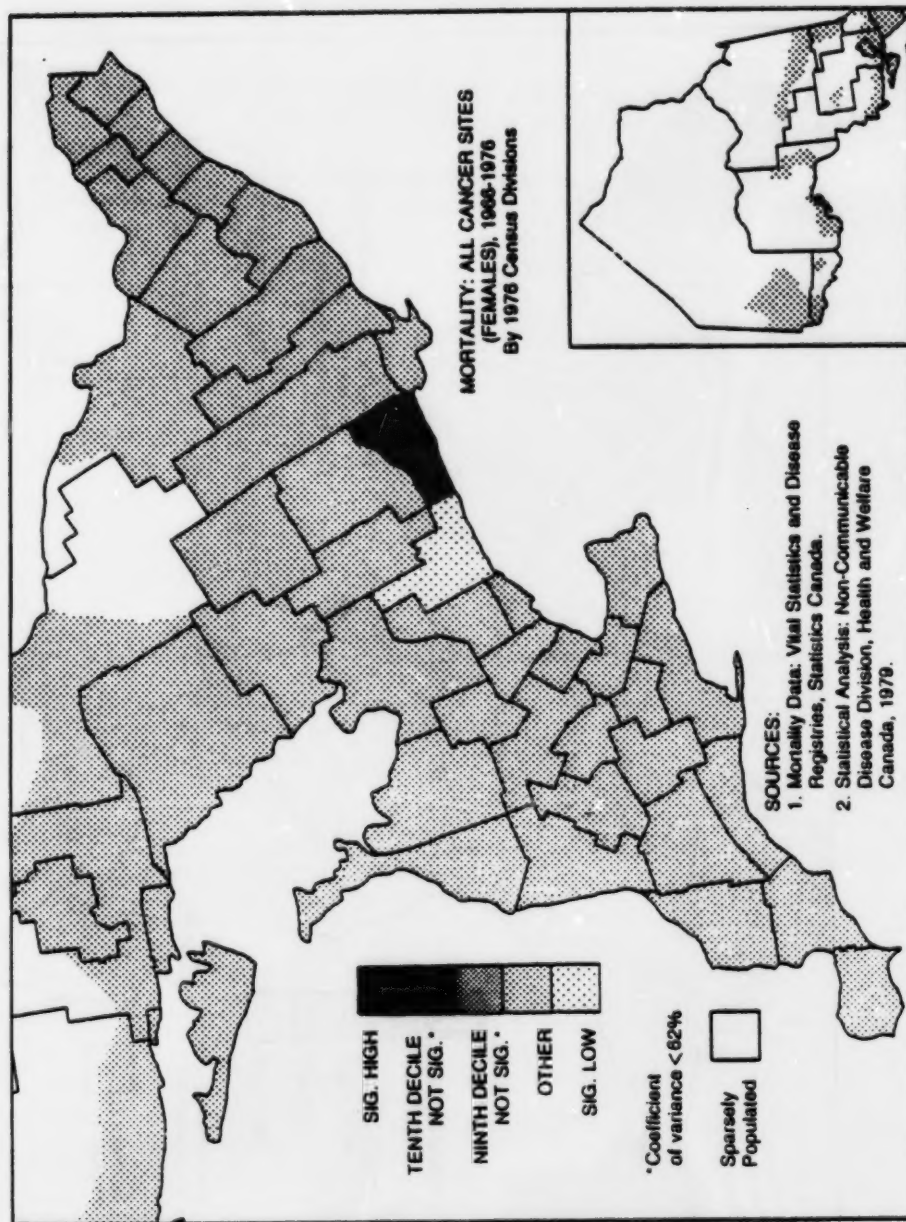
The following maps show cancer rates in Ontario, by census division. The maps show that in some locations there is a greater risk of death from cancer than in others. There is no obvious explanation for this variation. The higher male mortality figures in the Toronto, Hamilton and Niagara Falls regions could be related, in part, to the nature of the industrial work in those areas from which there can be increased occupational as well as environmental carcinogenic exposure. However, such differences between highly industrialized and more rural areas have been noted elsewhere. Most investigators have found that the differences can be primarily attributed to differences in cigarette smoking in the various areas.

Lessons

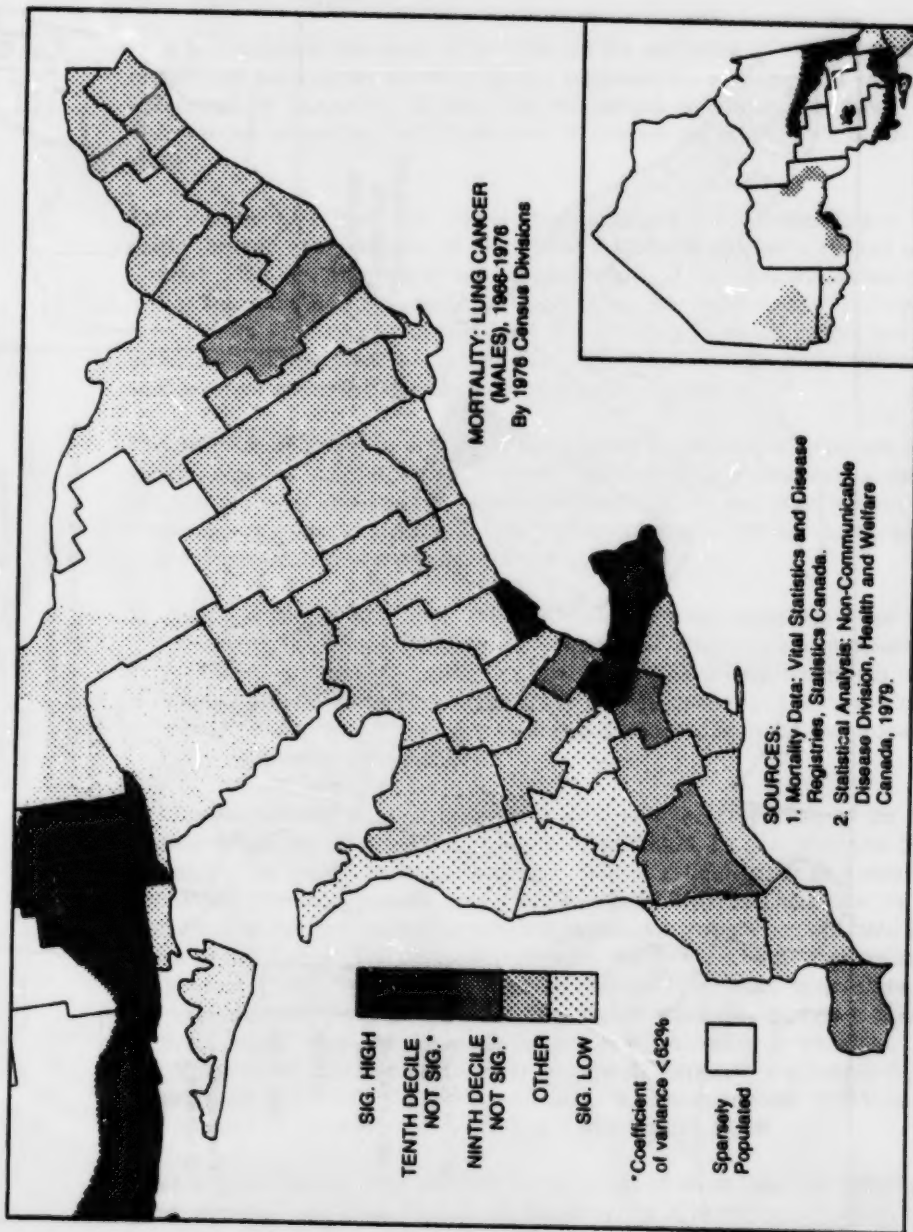
1. The widely-held belief that changes in lifestyle have led to an increase in cancer is valid in Ontario for lung cancer, and is attributable mainly to cigarette smoking.
2. Another major identifiable change affecting the incidence of cancer in Ontario is the increase in the elderly as a percentage of the total population.



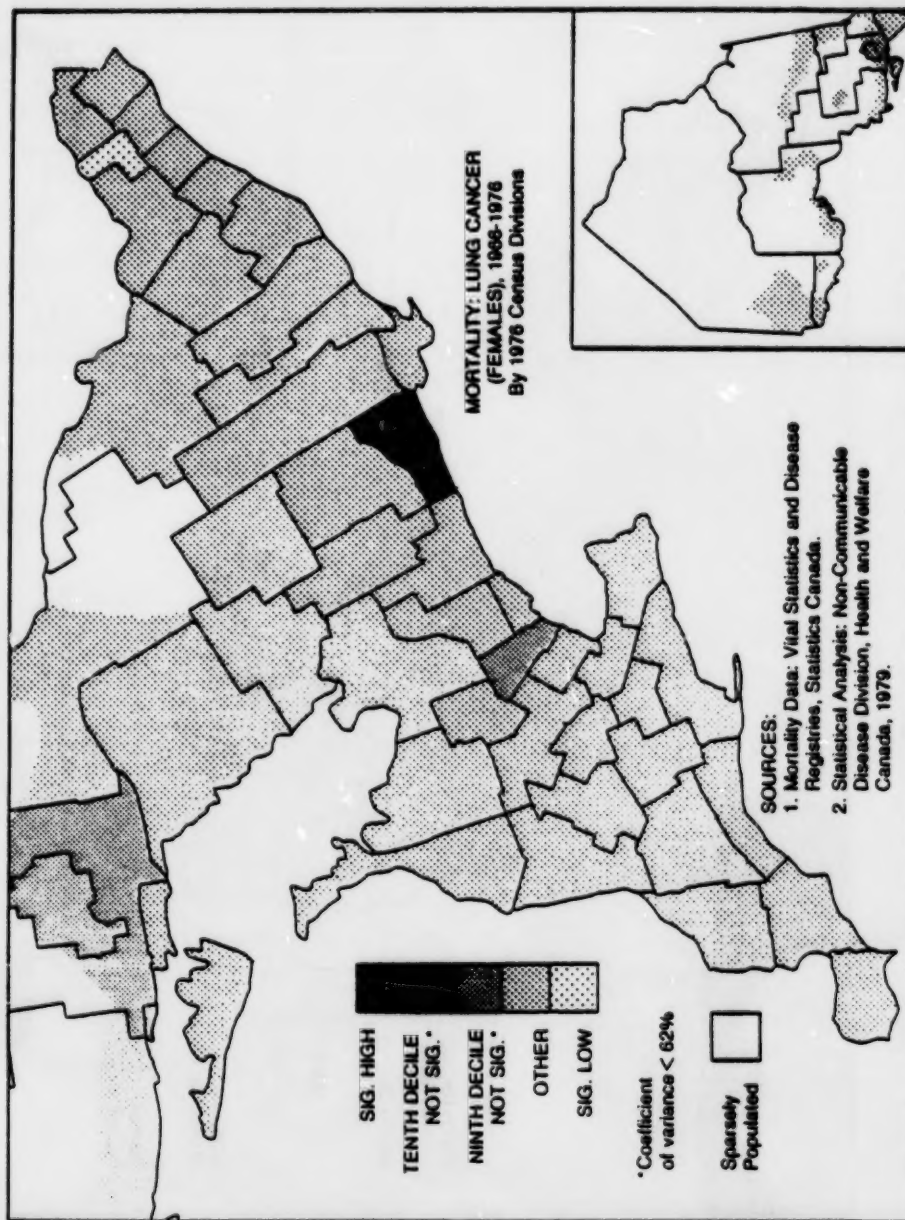
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by the Geocartographics Group, Statistics Canada, 1981.



Produced for the Advisory Council on Occupational Health & Occupational Safety, Ontario,
 by the Geocartographics Sub-Division, Statistics Canada, 1981.



Produced for the Advisory Council on Occupational Health & Occupational Safety, Ontario, by the Geocartographics Group, Statistics Canada, 1981.



Produced for the Advisory Council on Occupational Health & Occupational Safety, Ontario,
by the Geocartographics Sub-Division, Statistics Canada, 1981.

5. ASSESSMENT OF RISK FACTORS

Epidemiological studies indicate different rates of incidence for certain types of cancer in different areas of the world. For example, Japan has an extremely low rate of breast and colon cancer and a high rate of stomach cancer. The reverse applies in Canada. Japanese immigrants to North America show, within a generation or two, the cancer incidence patterns characteristic of the North American population. These and related facts have led John Higginson¹ to state that:

'...it is concluded that these differences (in the incidence of various tumours in different parts of the world) probably represent the proportion of cancers influenced by exogenous factors. The conceptual significance of these observations indicating that 90 per cent of cancers are preventable is obvious.'

This statement has been the subject of considerable misunderstanding—partly through overemphasis of the role of manufactured chemicals and industrial pollution. Higginson¹ has recently clarified the intention of his earlier statement and indicated that in his terms the 'environment' ('exogenous factors') represents the sum total of the milieu in which people live including 'lifestyle factors' such as diet, cigarette smoking, sexual habits as well as more obvious exposure to carcinogenic substances.

The problem of trying to determine the relative importance of exposure to various types of carcinogens is extremely difficult, but is obviously a matter of great practical importance. Among the complexities that must be reckoned with in trying to assess the relative importance of various carcinogens in causing human cancer are the following:

- 1) there is a latency period of five to 40 years between initial exposure to the agent(s) that causes cancer and the clinical appearance of tumours,
- 2) except in very extreme cases (see case history on β -naphthylamine), only a small proportion of those exposed to a given carcinogen will develop cancer. The effect of exposure to carcinogens is to increase the probability of tumours developing.

In some circumstances, it is possible to determine the proportion of the disease which can be attributed to a particular factor. This is best done by comparing the incidence of (or mortality from) a given tumour in a population which has been exposed to a particular factor with the incidence (or mortality) in another otherwise matched population, which has not been exposed to this factor. The difference between the two rates will then indicate the amount of the disease that can be attributed to the factor in question. For example, since the incidence of lung cancer amongst smokers is about 10 times higher than that for non-smokers, it is reasonable to conclude that 9 out of 10 cases of lung cancer in cigarette smokers are due to the carcinogenic stimulus of cigarette smoke. It is also reasonable to conclude that one out of 11 would have developed without this factor.

Since a given tumour may develop as the result of more than one carcinogenic stimulus (see Case History on Smoking), it is better to talk about 'risk factors', each of which increases the probability of a tumour developing at a particular site in a particular individual, than to speak of the 'cause of

cancer'. An asbestos worker who smokes is exposed to two identifiable risk factors—tobacco smoke and asbestos. From the data of Hammond *et al.*,³ it appears that the risk of a smoker who is not occupationally exposed to asbestos developing lung cancer is almost 11 times that of a non-smoker who is not exposed to asbestos, and that the rate for asbestos workers who do not smoke is 5.2 times that of persons who neither smoke nor are exposed to asbestos, while for those who both smoke and work with asbestos, the risk is 53 times that of the unexposed non-smoker. In this situation and in others, such as bladder cancer, where a number of individual agents are well recognized as risk factors, the sum of the various attributable fractions may easily exceed 100 per cent. This is just an indication of the extent to which a cancer has resulted from the interaction of more than one causal factor.

Finally, it should be clear that, in general, it is not possible to state with any certainty exactly what agents were responsible for the development of a given tumour in a particular individual. The best that can be done is to suggest the relative importance of various risk factors.

In spite of the difficulties involved, various groups have tried to make estimates of the relative importance of factors such as 'lifestyle' (diet, smoking habits and the like) and occupational exposure to the total cancer burden of the general population. The conclusions reached differ widely and the lack of agreement reflects both the difficulty of the problem and the scarcity of the necessary data to provide definitive answers. At one extreme are those like Wynder and Gori,⁴ who attribute only five per cent of cancer in males and two per cent in females to occupational factors, while at the other extreme, are those (see for example, the 1978 US NCI, NIOSH, NIES report, reprinted in reference #7) who believe that 20 per cent or more of cancer may be occupational in origin. The papers presented at a meeting devoted to the quantification of occupational cancer, held during March 1981, have just been published.⁵ In the United Kingdom, Fox and Adelstein,⁶ using the Registrar General's figures on occupational mortality in 1970-72, attempted to answer the question of how much mortality of an occupational group reflects work environment and how much, way of life. Their analysis suggested that, overall, some 18 per cent of the variation in mortality rates between occupational groups was occupationally related—more than 80 per cent of the variation being related to social class. Twelve per cent of the variation in cancer mortality rates appeared to be associated with work.

Given data such as the Ontario cancer rates presented above, it seems reasonable to conclude that the recent development of industrial chemicals and processes has not caused a new epidemic of cancer in the population as a whole. Such a conclusion is similar to one recently reached by Doll and Peto,⁷ who reviewed trends in mortality from cancer in the United States from 1933 to 1978. There is, however, one proviso that must be noted here, namely that since the latent period for the development of human cancer is long, the full consequences of a new carcinogenic substance will not be apparent for many years after its first introduction. Thus, it is conceivable that there may yet be a significant increase in cancer due to chemicals introduced in the past 15 to 25 years. Only time will provide a definitive answer.

The conclusion that there is no real evidence for an increase in the age-adjusted incidence of cancer in the general population should in no way be taken as a reason for downgrading the importance of occupational carcinogens. Indeed, it should be clear that in situations in which the combined risks from an occupational factor (e.g. asbestos) and a 'lifestyle' factor (e.g. smoking) are more than additive, removal of *either* factor alone will cause a dramatic reduction of the risk. To go back to the data of Hammond *et al* on smoking asbestos workers, one can estimate that in that particular population with those degrees of risk, removal of the smoking factor *alone* could prevent 79 per cent of the lung cancer, while removal of the asbestos factor *alone* could prevent 90 per cent of the cancer.

Occupational cancer hazards are much greater for small groups of workers who are exposed to relatively high levels of carcinogenic agents, and thus might not be detected in provincial statistics. Procedures are needed which will facilitate the detection of carcinogens in the workplace. In addition, continued industrial innovation results in the introduction to the workplace of several hundred new compounds each year, and policies are needed to ensure that such compounds have been tested for potential carcinogenic hazards.

It must be recognized that, as was shown in the case studies, significant efforts have been made to reduce exposure and these should have an effect, over the course of time, on the incidence of cancer related to workplace exposure.

Lesson

There is no convincing evidence that there has been, at least up to the present time, any significant increase in cancer in the population as a whole, due to chemicals introduced in the last 15 to 25 years. This does not mean that occupational cancer hazards are unimportant, but that they must be dealt with by the detection and control of carcinogens in the workplace, not by monitoring provincial statistics for the general population.

6. CANCER IN THE WORKPLACE IN ONTARIO

The data do not exist to permit a reliable estimate to be made of the percentage of cancer deaths in Ontario which can be attributed to occupational exposure to carcinogens. The only statistics available in this area are those produced by the Workmen's Compensation Board.¹⁰⁰ In assessing the significance of statistics on accepted claims related to occupational cancer, two factors must be borne in mind:

1. The delay in recognizing workplace hazards as being possible causes of cancer, and
2. The fact that the Workmen's Compensation Board figures probably do not reflect the true extent of the problem. Because of the sometimes lengthy latency period between exposure to a carcinogen and the development of cancer, an exposed worker may have moved to another occupation and, as a result, may find it difficult to establish his or her claim. The worker may not even know that he/she has a claim.

During a 35 year period from 1947 through to December 31, 1981, the Workmen's Compensation Board of Ontario accepted 588 claims related to occupational cancer. Four hundred and three of these claims were related to lung cancer. A breakdown of this figure shows 85 related to radon gas, 165 related to nickel sintering operations, 59 related to asbestos fibre dust, 33 related to arsenic, 16 cases related to coke oven operations, 12 cases related to one company (Consumers' Gas) in Toronto many years ago where commercial and domestic gas was developed utilizing coking processes, 27 cases from DOFASCO operations and six from other foundries.

During this same interval, the WCB has accepted 57 cases of sinus cancer related to nickel sintering operations.

Fifty-one cases of mesothelioma related to asbestos fibre dust have been identified.

Nine cases of gastrointestinal cancer have been accepted for compensation as being related to asbestos fibre dust exposure.

Fifteen cases of laryngeal carcinoma have been accepted, ten of which have been related to nickel aerosol exposure in smelting operations and five have been related to asbestos fibre dust exposure.

Forty-three cases of skin cancer have been accepted. These have multiple causation including radiation, exposure to cutting oils, chronic traumatic ulceration, etc.

Five cases of bladder cancer have been accepted. These were related to aniline dyes.

Four cases of leukemia have been accepted. These have multiple causes including radiation and exposure to benzene.

One case of synovial sarcoma has been accepted.

Lesson

To date, the identification of carcinogens has been dependent upon work-place exposure and the subsequent identification of cancer in members of the work force. We are now faced with the challenge of designing a system to control substances which could contribute to the development of cancer, so that the work force need not be exposed. An alternative method of identifying carcinogens must be employed—one which can provide advance warning of a hazard and which is not dependent upon the results of the exposure of a human population.

7. SCREENING FOR CARCINOGENS

Until recently, our limited knowledge of cancer and carcinogens made it difficult to develop approaches that might predict whether a chemical was a potential carcinogen. However, our increased understanding of the mechanisms of carcinogenesis has now made it possible to develop systems for screening new substances as possible carcinogens. Since it is widely accepted that prevention is one of the most important measures for preserving

the health of individuals, a key question is: Can these new tests be used to identify potential carcinogens and allow us to prevent inadvertent exposure of the work force?

There are two major approaches that are involved in the screening of carcinogens: short-term *in vitro* screening tests which are relatively cheap and quick to perform and longer-term more expensive animal tests.

1. Animal Tests

a) Long-term Animal Tests

The most reliable and generally acceptable index of cancer-inducing properties of chemicals in humans, next to the study of humans, is the induction of cancer in experimental animals. The basis for the general acceptance is the increasing realization that animals, especially mammals, react to toxic substances very much as humans do. This includes both acute reactions and long-term ones such as cancer development. Even though cancer may take up to one-fourth or one-third of the life span of any species to develop, and involves many steps, the similarities between experimental animals and humans in their reactions to cancer-inducing chemicals are many. For example, of some 30 or more chemicals or chemical mixtures known to induce cancer in humans, only one, arsenic, has failed in long-term animal tests. This high index of reliability makes the long-term animal bioassay for carcinogenicity attractive as the most acceptable test, and generates a comfortable reliance on its predictability. It is only prudent to assume that any chemical that is proven to be cancer-inducing in an experimental animal, may also be so in humans.

However, the animal bioassay, to be reliable, must be done with care and under expert supervision. Since animal species may differ very much in their sensitivity to toxic agents, including carcinogens, and since no single species or group of species resembles the sensitivity of humans more than any other, it is preferable to test the chemical in at least two species.

Also, since cancer may take a long time to develop, sufficient numbers of animals must survive for a sufficient period to allow for this development. Also, since many toxic agents, including carcinogens, may show a sex difference in the development of toxic responses, adequate numbers of animals of each sex should be included.

These are a few of the important factors that must be included in any adequate test for cancer development. This necessitates high quality animal facilities, highly competent pathologists familiar with cancer in animals as well as in humans and careful long-term supervision of the animals under hygienic conditions.

These and other requirements have been outlined as guidelines by the National Cancer Institute¹³ in the USA. These guidelines have indicated to industrial and academic centres what constitutes a reliable bioassay procedure and have had an important influence in setting standards.

Unfortunately, the requirements are such that the present cost to test a single chemical may be from \$250,000 to \$500,000. With this cost factor and with a time period of about two and one-half to three years before an answer is obtained, the importance of the short-term tests becomes evident.

It has been shown in many studies that inert fibres such as asbestos and glass wool will induce mesotheliomas of the pleura or the peritoneum when injected into suitable experimental animals. It must be emphasized that unlike most of the 'usual' chemical carcinogens, these remain in the tissue for a long period of time. The problems relating to the regulation of cancer inducing fibres must clearly be different from those relating to the regulation of chemicals that have a relatively brief sojourn in the body.

b) Short-term Animal Tests

Because of the similarities in the toxic responses of humans and animals, it is desirable that tests for potential carcinogenicity be as closely related as possible to the end stage, cancer. This can be done by the use of an early reaction of an animal to a potential carcinogen and one that consistently precedes the appearance of cancer. So far, only very few such tests have been proposed.

The end-points in these are damage to DNA induced by a potential carcinogen, the repair of the DNA following such damage or the induction of altered cells that can be stimulated to grow and that are precursors for later steps in cancer development. These are largely underdeveloped. They have many attractive features, including the cost that is not much more than that involved in *in vitro* tests using bacteria or cells in culture. These short-term tests in intact animals, especially the one involving altered cells, might prove to be extremely useful for following the development of chemicals that in one form may be mutagenic but can be modified to eliminate the mutagenic capacity. In addition, the use of short-term animal tests offers a comfortable bridge between the *in vitro* tests, which are very difficult to relate directly to cancer, and the induction of cancer.

2. Short-term In Vitro Tests

a) The needs

As mentioned above, conventional animal carcinogenicity assays are expensive, laborious and time consuming. Since there are large numbers of untested chemicals currently in use and many new ones are introduced each year, the development of so-called 'short-term' assays that can detect potential carcinogens has been a matter of great interest. Although the concept is little more than a decade old, dozens of tests have been proposed.

b) The 'concept'

Essentially, all current short-term tests have as their basis some means of detecting damage to DNA in a test organism. The organisms employed range from bacteria, through yeast and cultured mammalian cells, to rodents, while the biological 'end-points' used to detect and quantify DNA damage involve mutation, breakage of DNA, endogenous repair of DNA damage by the test compounds, chromosome damage, etc. It is well established that

many carcinogens must be metabolized before they damage cellular constituents. Since bacteria and many cultured mammalian cell lines lack the enzymes required for this process, preparations from mammalian liver are frequently added to provide for 'metabolic activation'. Alternatively, 'host-mediated' assays may be used in which test micro-organisms are injected into an animal (which is exposed to the test compound) and, after a suitable period, recovered and assayed for mutations. Various test systems and the end points involved are shown in the following table. Detailed consideration of these tests has been presented by the International Agency for Research on Cancer¹¹ and by Weisburger and Williams¹².

'Organism'	Metabolic Activation	End Point
Bacteria:		
<i>Salmonella typhimurium</i> (the 'Ames Assay')	Liver S9 preparation	- reverse or forward mutation
<i>Escherichia coli</i>	Liver S9	- reverse or forward mutation
Fungi:		
<i>Saccharomyces cerevisiae</i> (yeast)	endogenous	- gene mutation - gene conversion
<i>Neurospora crassa</i>	endogenous	- gene mutation - gene conversion
Mammalian cells:		
(in long term culture) eg. CHO (Chinese hamster ovary); L5178Y mouse lymphoma; Human fibroblasts	Can be supplied by Liver S9	- gene mutation - DNA repair - <i>in vitro</i> sister chromatid exchange - transformation (except human cells)
Primary hepatocytes	endogenous	- DNA repair
Intact animals		
rat liver	endogenous	- pre neoplastic enzyme markers
rodents	endogenous	- <i>in vivo</i> sister chromatid exchange

c) Some Examples

While it is not the purpose of this document to provide a comprehensive account of the short-term assays currently available, a few examples will illustrate the development and application of some of the important tests.

(i) *Salmonella*/S9 assay (Ames assay)

The strains of bacteria used in the *Salmonella*/S9 assay are mutants of *Salmonella typhimurium*, which were developed by Dr. Bruce Ames and his colleagues at the University of California, Berkeley. These test strains are unable to synthesize an essential amino acid called histidine and, therefore,

will not multiply and grow into visible colonies unless exogenous histidine is provided in the medium. However, these bacteria can revert to histidine independence through mutation. Mutagenic chemicals increase the rate of mutation and, hence, increase the number of bacteria that are able to grow into visible colonies. It is worth noting that these test strains have been developed so that they will be very sensitive to mutagens. In addition to the original carefully chosen mutation to histidine dependence, additional mutations have been added which a) block DNA repair, b) increase the permeability to large molecules, and c) in some strains the pKM101 plasmid has been added to increase the amount of mutation produced by a given amount of DNA damage.

Since, as noted above, many carcinogens are not active until they have been metabolized by enzymes found in animal tissues but not in bacteria, it is necessary to add appropriate animal enzymes to the test plates. This is done by use of the 'S-9 fraction' from rat liver. A useful feature of this assay system is provided by the existence of strains which respond only to particular classes of mutagen and are totally unresponsive to others.

The Salmonella/S9 assay has been subjected to very extensive validity studies and there is general agreement that it works well with strong carcinogenic 'initiators', but may give false negatives with some other carcinogens such as organochlorine compounds, azo compounds and carcinogenic hormones. The test also gives 'false positives' with some compounds which are not considered to be carcinogenic.

Commercial laboratories currently quote about \$1,000 for the thorough testing of one substance in the Salmonella/S9 assay. The time required is less than one week.

It is worth noting that the same strategy, including the addition of S9, can be used to detect mutation in cultured mammalian cell lines. However, somewhat longer times are generally involved.

(ii) *DNA repair in primary hepatocyte cultures*

Hepatocytes (i.e. liver cells) are easily prepared from the liver of animals such as rats. These cells remain 'alive' for several days but do not grow and divide. Nevertheless, they offer advantages as short-term test 'organisms' since they contain many of the mammalian carcinogen-metabolizing enzymes and, unlike the situation that obtains in S9 preparations, these enzymes are in their normal cellular environment. Thus, hepatocytes are able to 'activate' a wide range of carcinogens so that they damage DNA. Other enzymes in the hepatocytes recognize DNA damage and begin repair processes which result in the physical removal of much (but not all) of the damage and the subsequent resynthesis of the DNA chain from low molecular weight building blocks. The repair process can readily be detected if one of these building blocks (thymidine) is radioactively labelled and supplied in the medium. Cells whose DNA has been damaged and at least partially repaired will be radioactive. The DNA of unexposed cells will not be radioactive since it, being undamaged, is not subject to 'removal: resynthesis' repair. This assay has been less extensively validated than the Salmonella assay, but appears at this stage to be very useful at least in a qualitative sense. The cost of the repair assay would be a few thousand dollars per compound and

the time involved may be one week (if scintillation counting is used) or several weeks if autoradiographic techniques are used.

(iii) *Sister chromatid exchange*

This assay measures the reciprocal exchange of material between the two chromatids (strands) of a mammalian chromosome. Such exchanges (which can be induced by radiation and mutagenic chemicals) are readily detected by well established cytogenetic procedures. Sister chromatid exchange can be measured either in established cell lines *in vitro* or in intact animals whose bone marrow or lymphocytes can then be examined. (Indeed, the use of blood lymphocytes makes it possible to determine the frequency of sister chromatid exchanges in cells from humans who have been exposed to radiation or chemicals).

Unfortunately, neither the molecular basis for sister chromatid exchanges nor their exact relevance to mutagenesis or carcinogenesis has been established. Such exchanges are, however, generally interpreted as a consequence of damage to DNA and, thus, an indication of exposure to potential carcinogens. Because of the need to score large numbers of cells under the microscope, this test takes several weeks and costs several thousand dollars per chemical.

d) Current Status

Short-term tests are still at a stage of rapid development and improvement. It will be clear from the examples presented above that compromises are made in devising such assay systems. Those assays which involve bacteria or cultured mammalian cell lines have the advantage of a fast and easily detected end-point, but are far removed from the normal pharmacological processes which take place in an intact animal. While addition of S9 preparations provides many of the relevant enzymes, it does not provide the full repertoire of mammalian biochemistry. The *in vivo* test systems also have limitations since they depend upon the active carcinogen getting to and damaging the tissue which is later to be examined, e.g., liver in the case of the assay employing 'pre-neoplastic' enzyme markers or bone marrow for the *in vivo* sister chromatid exchange assay.

Nevertheless, even at this stage, intelligent use of short-term tests can offer a significant degree of protection to workers who are to be exposed to new chemicals. With the present state of the art, one can anticipate that most (perhaps 80 per cent or more) of strongly carcinogenic materials can be detected. While it is to be hoped that the predictive value of short-term assays can be improved, the detection of something like four out of five carcinogens amongst new chemicals in the workplace would represent a substantial improvement over the current situation, where such materials are largely unregulated.

e) Short-term Tests in Human Population Monitoring

(i) *Urine Mutagenicity*

The foregoing section has reviewed the use of short-term assays as a means of screening chemicals for potential carcinogenic or mutagenic hazards to humans. Another use for some of these assays may also prove to be of importance in occupational settings. This involves monitoring human urine for mutagenic activity, or human cells for chromosome damage.

The Ames assay provides a sensitive means of detecting and quantitating the presence of mutagens in the urine of humans. The assay was first used in this way to show that smoking resulted in urinary mutagens (which may well be responsible for the excess bladder cancer seen in smokers). Similarly, mutagens have been detected in the urine of rubber workers and cancer chemotherapy nurses (who handle cytotoxic and carcinogenic drugs). The costs of the test on urine are roughly the same as for pure chemicals and depend in part on the number of strains to be used. In addition, the mutagenic material from urine must be concentrated using non-ionic resins. In such cases, urinary mutagenicity provides direct proof that human tissues are being exposed and gives at least a rough measure of the level of exposure. Further, in such situations, monitoring of urinary mutagens provides a means of assessing the success of any measures introduced to decrease exposure. It should be noted that one cannot expect all mutagens to which humans are exposed to accumulate in the urine since some will be so reactive they 'disappear' completely before there is time for excretion, while others may be metabolized completely to non-mutagenic products before they appear in the urine or may be excreted by other routes. Even in situations in which mutagenic activity is excreted in the urine, it will be cleared from the body fairly rapidly so that sampling times must be chosen judiciously. Then too, there are the inherent limitations of the assay which make it relatively insensitive to some chemical classes of mutagens. Thus, the absence of urinary mutagenic activity does not necessarily mean lack of exposure. The important point is that the presence of urinary mutagens is clear and unequivocal evidence for exposure. Much work is currently being done to assess the potential of such assays in occupational settings.

(ii) *Cytogenetics*

A second approach utilizing material from humans is cytogenetic determination of chromosomal damage. The cells employed are lymphocytes, which can be cultured from blood samples. Thus, the test cells are obtained directly from humans and increases in damage can be attributed to exposure to chromosome-damaging agents. Three end-points have been used: 1) chromosome aberrations, 2) micronuclei (derived from fragments of chromosomes) and sister chromatid exchanges (see previous section). Cytogenetic studies have shown an increase in chromosome damage in heavily exposed vinyl chloride workers and in humans exposed to ionizing radiation. At least in the latter case, it is established that increased chromosome damage in a population is indicative of an increased cancer risk for that population. However, the extent of cytogenetic damage in a given individual is *not* a predictor of the risk of cancer for *that individual*. Again, it is not to be expected that all potential carcinogens will cause cytogenetic changes in lymphocytes. The utility of these assays in occupational settings is currently

receiving considerable attention. Chromosome aberrations are most often unstable and the abnormal cells are gradually lost from the peripheral blood circulation with time. For this reason, 'excursion' exposures require immediate follow-up with sample collection (within 24 hours of exposure). Chronic exposures probably could be detected at any time after sufficient exposure.

Cytogenetic studies are expensive since even to detect a substantial difference in chromosome damage between an exposed and an unexposed population requires at least several dozen individuals in each group; estimates range as high as \$1,000 per individual examined.

(iii) Induced Mutations

Lymphocytes can also be used to assess human exposure to mutagens by determining biochemically the frequency of cells which are resistant to certain drugs. (In normal humans the frequency of drug-resistant lymphocytes is low; exposure to mutagens such as anti-cancer agents causes a marked increase in resistance and it may be possible to use the frequency of drug-resistant cells as an index of exposure). This technique offers the promise of complementing the measurement of gross chromosomal damage provided by the cytogenetic assays described above with information on more subtle effects on particular genes. So far, the procedures used to estimate drug resistance are laborious and, as a result, the costs are high.

(iv) Sperm Abnormalities

In animal semen, the frequency of sperm having abnormal shapes is known to be increased by exposure of the animals to some (but by no means all) mutagenic and carcinogenic compounds. Thus, we have another readily available source of human (male) cells which can be scrutinized to try to determine the consequences of exposure of men to a particular environment.

Sperm samples can also be used for the 'fluorescent Y' chromosome test. Normal sperm contain either zero or one Y chromosome and the presence of sperm with two Y chromosomes is indicative of 'non-disjunction' (i.e. failure of the mechanism which normally ensures that one of each pair of newly replicated chromosomes goes to each daughter cell). This process represents a different type of genetic problem from mutation and chromosome breaking.

3. Promoters

There is, at present, no generally accepted way of screening for promoters, either with animal or short-term tests. It is, therefore, important that research be encouraged in this area.

Lesson

Since prevention is one of the most important measures for preserving the health of individuals, a major issue is how best to identify potential carcinogens and promoters and prevent inadvertent occupational exposure. The most reliable tests are still those conducted on animals. Intelligent use of short-term tests offers an attractive, faster and less expensive alternative.

However, these tests have only been developed very recently and new ones are still appearing. Their strengths and weaknesses are still not fully appreciated, and practical experience with them is still quite limited.

8. SUMMARY OF TESTING REQUIREMENTS

Past experience has shown that a small fraction of the chemicals introduced into industry have been carcinogenic. There is no reason to expect that this situation will change unless deliberate interventions are made. All reasonable steps should be taken to minimize the chance that workers will be exposed to new chemicals whose carcinogenicity will be appreciated only after 20 years or more, when cancer appears in the work force. Ideally, extensive animal and short-term tests would be required. Properly conducted, such assays would detect most, but certainly not all, potential carcinogens. However, as stated above, capacity for animal testing (even if the necessary funds could be provided) is inadequate. We must, therefore, fall back upon a battery of short-term tests, recognizing that this strategy should detect most strong carcinogenic initiators, but will be less effective than comprehensive animal tests. As additional short-term tests are developed that increase the range of carcinogens which can be detected, these should be incorporated into the required battery.

1. In Vitro Short-term Tests

We recommend that, as a minimum, two different short-term tests be required. In general, we would expect one of these to be an assay for point mutations in bacteria or a simple eukaryotic organism like yeast (with and without an added activation system) and the other to be an assay which would detect chromosomal breakage or rearrangement in cultured mammalian cells (again with provisions for metabolic activation). Inclusion of other assays such as those for DNA repair will often provide additional useful information. Specific assays should be selected with due regard for the performance of the assays with compounds analogous to those being tested.

We recommend further that these tests be carried out on commercial samples of chemicals rather than (or in addition to) tests on purified preparations since there is abundant experience to show that impurities, rather than the major constituent, may be responsible for the carcinogenic properties of industrial chemicals. Since the whole area of short-term testing is evolving rapidly, we also recommend that the requirements for the use of such tests be reviewed by the ministry every three years.

New chemicals which are closely related to others that are already in use should not be exempted from the testing requirements recommended above. Since isomeric pairs of organic compounds can differ very widely in their properties (e.g. β -naphthylamine and benzo(a)pyrene are both powerful carcinogens while their isomers [α -naphthylamine and benzo(e)pyrene] are weak or non-carcinogens), we recommend that tests be required on all new organic compounds.

2. Long-term Animal Tests

Animal bioassays must be conducted with care and under expert supervision. We recommend that such tests be performed in two species, using adequate numbers of animals of each sex. We recommend that the requirements outlined by the National Cancer Institute (USA)¹³ be followed, as constituting a reliable bioassay procedure.

3. Advisory Committee

It is not possible to make arbitrary rules to deal with all possible outcomes of test results. For example, what should be done with a chemical which gives, say, a positive result in a bacterial mutagenicity assay but negative results with *in vitro* chromosomal tests and in animal cancer bioassays? In some cases, it may be clear that the probability of risk to humans is so low that the substance should be regarded as non-carcinogenic. There may be need for an advisory committee to examine the results obtained with such compounds and to recommend the category into which they should be placed.

9. PRINCIPLES OF EPIDEMIOLOGICAL SURVEILLANCE

Evidence as to whether a substance is carcinogenic or not can be derived, as this report indicates, from a number of sources. Epidemiological data from human studies have been an important source of information in providing evidence on the carcinogenicity of a number of substances encountered in the occupational environment. Indeed, classically, the first studies which identified the risk to humans of occupational exposures arose from the application of the epidemiologic method.

Epidemiologic evidence can be obtained through three broad approaches. Each of these varies in terms of the ease with which the studies can be carried out and the strength of the evidence. The approaches involve:

1. Evidence derived from descriptive studies of the occurrence of cancer in humans in relation to time, place and person.
2. Evidence obtained from analytic epidemiologic studies of the case-control or cohort type.
3. Evidence obtained from well-conducted intervention studies in epidemiology, especially utilizing the methodology of the randomized controlled trial.

1. Descriptive Epidemiologic Studies

Studies of this type are often called 'hypothesis derivation studies'. In their simplest form, an observation is made that a cluster of cases is occurring which general experience would suggest to be unusual. For example, although the carcinogenicity of vinyl chloride was first established through animal studies (see Case History), the significance of these observations was not appreciated until a physician noted a cluster of cases of a rare tumour (angiosarcoma of the liver) in a group of workers from one particular plastics manufacturing plant. A number of similar examples can be given: thus, the first clue may come from the observation of 'alert clinicians'. More precise descriptive studies come from comparisons of the incidence of

(or mortality from) cancers at particular sites, occurring in different countries or in different areas or time periods within countries. Comparisons of incidence demand an established population-based cancer registry; comparisons of mortality require an established vital statistics system. Providing the necessary data are supplied, such comparisons can often be extended to the incidence in or mortality of different types of individuals, most obviously on the basis of sex, but also on the basis of race or colour. In the last decade in Canada, such descriptive studies have been placed on a more formal basis whereby the incidence and mortality of cancer is being monitored on a census district, or county level. Already, such studies have indicated unusual occurrences of cancer that might have an occupational basis.

2. Analytic Studies

In recent years, case-control and cohort studies in epidemiology have been brought to a high state of precision. In cohort studies, individuals exposed to a factor considered likely to increase the risk of disease are followed forward in time with a comparable group of non-exposed individuals as a control. The incidence of cancer (or less satisfactorily, the mortality from cancer) is directly compared between the two groups. Various modifications of this approach are possible. Thus, if records are available of complete groups of individuals exposed to a factor from some time in the past, then it is possible to reconstruct the history of this cohort of individuals and analyse incidence and/or mortality of cancer up to the present time. Such an approach may have a number of advantages, both in terms of lesser expense and more timely ascertainment of results, particularly in cancer with a long latent period to be expected from first exposure to development of the disease. It may also be subject to a number of different biases, particularly if there is doubt on the extent to which the original set of records is complete. It may also prove difficult in both historical cohort studies of the types just described and standard cohort studies with follow-up from now to the future to establish an appropriate control group for comparison purposes. In a number of occupational studies, the experience of the general population has been used for comparison, but to the extent that the exposed group differs from the general population in factors other than the exposure of interest, the resulting finding may be misleading.

In case-control studies, the point of departure is the diagnosis of the case of disease. Generally through the interview method, a detailed history is then obtained of lifetime exposure to the factors of interest, and comparison made with comparable individuals free of disease who may be drawn from hospital or general population groups. If the case series is representative of the general population, the control series should be also. This method, though more economical than the cohort approach, is subject to biases of errors of recall. Particularly under some circumstances applicable in the occupational situation, it is possible for individuals who have developed cancer to recall more readily exposure to possible factors of interest as causes, than it is for control subjects to do so. Recall bias of this type has to be specially guarded against when extensive publicity surrounds a factor considered likely to be at risk for occupational cancer.

In general, in spite of its expense, the cohort approach has been preferred to the case-control approach for occupational studies. The main reason has been the ready availability of groups of exposed individuals whose experience has been reconstructed up to the present time. In a number of instances, for example, risks of asbestos, the findings from such historical cohort studies have subsequently been confirmed by the more standard cohort approach. However, increasingly, it has been appreciated that with common cancers and with the need to identify the extent to which different factors may be responsible for their etiology, the case-control approach may have many advantages. Thus, in one interview, it is possible not only to obtain a detailed occupational history, but a detailed smoking history and a detailed history of exposure to other possible risk factors, such as alcohol. Such data are rarely available in a cohort study, even in one set up in the classic mode prospectively. Indeed, because of the possibility that exposure to risk factors may change, for a classic cohort study to provide as much data as a case-control study in terms of different exposures, multiple interviews at different times are essential. This substantially increases the expense and few studies of this type have been performed. Further, with the availability of record linkage approaches, it has been appreciated that the cohort approach may enable some suspect risks to be identified in what becomes a hypothesis-seeking exercise with case-control studies utilized as the hypothesis-testing definitive study. The ready availability in Canada of facilities for record linkage of persons at high risk (see section Epidemiologic Surveillance of Persons at High Risk for Cancer) is likely to facilitate this type of approach materially in the future.

3. Intervention Studies

In general, the randomized controlled trial is accepted as having the least bias and provides the clearest evidence of whether a factor is, or is not, causal. However, for obvious reasons, it is virtually impossible to do such a study in the field of occupational health. Thus, even with the introduction of a new chemical, it is extremely unlikely that it would be possible to randomize individuals to be exposed, or not exposed, to it. Hence, a classic etiologic experiment cannot be performed. Nevertheless, it is possible that this approach may be increasingly used in the occupational situation in a manner which may help to confirm the importance of occupationally encountered risk factors. With a number of potential prophylactics against cancer being available, and with the need that their value be established using randomized controlled trials in individuals at high risk, it seems quite possible that a number of studies evaluating the use of such prophylactics in the occupational setting will take place in the next few years. Studies of this type, if they confirm the efficacy of a prophylactic, could be regarded as also providing further evidence of the importance of causal factors if the prophylactic was designed to counteract directly the effect of the suspected causal factor.

Criteria for Causality

A number of authors, but most particularly Bradford Hill,¹ have identified the criteria which permit the assumption of causality from epidemiological evidence initially being restricted to identified associations. These criteria are as follows:

Strength of the association (relative risk)

Consistency of the association

Correct temporality of the association (i.e. exposure precedes disease)

Biological gradient or dose response relationship

Plausibility of the association (i.e. consistent with biological knowledge)

Coherence of the association (i.e. it does not conflict with the known facts of biology and the natural history of the cancer)

Specificity of the association (i.e. the factor is associated with one disease)

Such a requirement is not an absolute one; indeed, it may not be found for materials including a large number of different carcinogens, for example, tobacco smoke.

Experimental evidence (i.e. evidence derived from a controlled clinical trial.) Although we have indicated above that such evidence may be impossible to come by in the occupational setting, an indirect approach to this can be found when exposure to a factor is removed in an occupational group and the risk of disease falls after an appropriate interval.

Lesson

Epidemiological data from human studies have been, and will continue to be, an important source of information about risk factors.

10. EPIDEMIOLOGICAL SURVEILLANCE OF PERSONS AT HIGH RISK FOR CANCER

While epidemiologic studies have been of crucial importance in detecting hazardous substances in the workplace, it is to be hoped that in the future there will be much less reliance on human exposure data in the identification of carcinogens. However, it is unlikely that screening procedures will be devised which will detect all carcinogens. Also, there could be categories of substances for which there is some suspicion, insufficient to justify their treatment as carcinogens, but justifying their careful surveillance.

The Advisory Council on Occupational Health and Occupational Safety¹⁴ has emphasized the need for exposure records for workers who have suffered a unique exposure to a dangerous or potentially dangerous environmental agent. The questions arise as to how such individuals can be kept under surveillance and how it can be determined whether or not they are indeed at increased risk.

The primary mechanisms for such surveillance are already in place in Canada, comprising provincial cancer registries established in each province that regularly submit their data to Statistics Canada and registrations of all deaths for which copies are submitted to Statistics Canada by provincial registrars of vital statistics. The death certificates have been consolidated into files accessible for computerized record linkage back to 1950, and the National Cancer Reporting System includes information on registrations with cancer from 1969 on. Record linkage procedures have been developed within Statistics Canada in collaboration with the NCIC Epidemiology Unit that facilitate inexpensive rapid computerized record linkage of incoming files with these two cumulative files of outcome (cancer registration or death certificate information). Cancer incidence and mortality rates among exposed individuals can thus be compared with the rates observed in unexposed individuals (whose files have been input at the same time) or with

the nationally reported rates. This system has already been used for a general assessment of occupational mortality and cancer incidence in Canada using the Unemployment Insurance Commission file for 1966-71 and for other studies of potential occupational hazards and non-occupational hazards such as exposure to ionizing radiation.

The basic requirement for utilization of this existing system is that those to be placed under surveillance must be fully identified in the file to be subsequently used for record linkage. Although identification by Social Insurance Number, which should always be available for occupationally exposed persons*, does provide the means to access personal identifying information through linkage with the Social Insurance Number master file, it would be preferable if the file combined Social Insurance Number with full personal identifying information because Social Insurance Numbers are not currently included on health records and will not be found on death certificates or many cancer registrations. Indeed, if the recommendation in the Report of the Commission of Inquiry into the Confidentiality of Health Information on the Unique Personal Health Identifier is accepted, the Social Insurance Number will not be included on health records. Thus, the Social Insurance Number alone cannot be used for record linkage purposes, personal identifying information having to be used instead.

The items of personal identifying information required include:

- full name with any name changes, particularly for women;
- full date and place of birth;
- mother's maiden name (if available);
- sex;
- marital status (if available);
- town or city and province of last known residence;
- Social Insurance Number;
- Health Insurance Number.

Exposure information should be as detailed as possible while details of prior exposures to other potentially hazardous occupations would also be desirable. If the exposure is believed likely to induce lung cancer, quantitative smoking information is highly desirable.

The other requisite for such surveillance is the continued existence of provincial cancer registries if the exposure is believed likely to have been carcinogenic. The Ontario Cancer Registry has itself been established by record linkage, initially manual and now computerized using routinely available sources of medical information. Unfortunately, in recent years, the registry has been somewhat starved of resources and, thus, although for the rest of the country cancer incidence is available up to 1978 and will shortly be available for 1979, data are only available for Ontario up to 1971, though it is hoped that data through to 1976 will shortly become available. The registry was initiated with the Ontario Cancer Incidence Survey for 1964-66. Because of the great importance of the registry, both in terms of identifying potential hot-spots using descriptive epidemiology and of providing the end-point of studies of workers under surveillance through computerized record linkage, it is essential that the appropriate resources be made available to the Ontario Cancer Treatment and Research Foundation to

*—until such time as a unique personal identifier other than the Social Insurance Number has been developed to facilitate the linkage of all records relevant to occupational health and safety.

ensure the registry's continuance. Indeed, because the foundation has a number of responsibilities, it might be felt appropriate to ensure that its budget include, as a line item, sufficient funds to ensure continuation of the registry so that it does not suffer from competition for funds for cancer treatment activities.

Because of the mobility of the Canadian population, and the desirability of ensuring that workers who migrate from Ontario continue to be followed if they have been placed at risk and are under surveillance, it is important that the record linkage be conducted with the national rather than the provincial files. Ontario is a beneficiary from the inclusion of the Ontario registry in the national system in having access to follow-up data from other registries as well as being the largest single contributor.

In order to establish whether or not the group under surveillance is at increased risk, record linkage of the file of exposed and, preferably, other non-exposed but comparable individuals would be performed at regular intervals with the two national data files (cancer registrations and deaths). Even if cancer incidence is the only end-point of interest, linkage with the death records is essential in order to determine the person-years at risk and to identify those who are no longer at risk because of death from other causes. Further, for non-cancer causes of interest that might be attributed to hazardous exposures, death from these conditions is, at present, the only outcome measure which could be evaluated using this system. With adequate identifying information, it can be assumed that if a link has not been made with one or other of the two files, the individual is still alive and has not developed cancer. There are two possible sources of error. One is failure because of paucity of identifying information to make an appropriate link. However, with a prospectively collected file and thus, opportunities for collecting adequate identifiers, this error should be minimal. The second is the possibility that some exposed workers may migrate abroad. When those who migrate to the United States (and are still regarded as Canadian residents) die, a copy of their death certificate is automatically forwarded to Statistics Canada, so that the fact of death would be identified through record linkage. This, however, does not apply to those who migrate to other countries; yet the numbers are believed to be very small and not likely to introduce any appreciable error in the comparison of observed numbers of events with those expected.

The nature and purpose of epidemiological surveillance will vary depending upon whether a known or suspect carcinogen is involved.

1. Exposure to Known Carcinogens

Here, an individual is known to have been exposed to an established carcinogen. The object of surveillance in this instance is to provide protection of the individual at risk. This principle is already established for radiation workers for whom exposure records are maintained and, in general, detectors to monitor exposure are worn. If, as will often be the case, it proves impossible to prevent the occurrence of cancer, such monitoring enables the provision of compensation for disease if it occurs in spite of precautions taken. It is essential that research into appropriate prophylactics and secondary prevention continue in such exposed populations.

2. Exposure to Suspect Carcinogens

Epidemiologic surveillance for suspect carcinogens will have to be designed on a population level. The objective here is to ensure that it is possible to determine through epidemiologic methods that increased incidence of disease did or did not follow exposure to the substance for which evidence on its carcinogenicity has not been precisely obtained. In many instances, it will be sufficient to maintain records at the individual factory or plant level and not require them to be collected regionally or nationally. Exposure records should be maintained in as much detail as possible, in order to identify those individuals who have been placed at possible increased risk. A difficulty with this sort of assessment will be the nature of the comparison group, i.e. the controls. In many instances, a general population comparison group may be inappropriate, it being more appropriate to make comparisons with individuals working in similar occupations in the same or different plants who have not been exposed to the suspect carcinogen. There may also be problems of assessment of confounding factors such as, for a number of cancers, cigarette smoking, and, as far as possible, therefore, the individual records that have been maintained at the plant level should contain notation of cigarette smoking as well.

In general, as already indicated, these records will not be collected centrally. Although industry may object to the cost of maintaining them, it is common experience that this type of record, though sometimes incomplete in terms of personal identifiers or cigarette smoking exposure, can generally be retrieved from well-managed plants. In other words, the information required for this type of surveillance is already being collected, often in computerized form. All that is needed, therefore, is that an additional reason for its collection be acknowledged for those exposed to known and suspect carcinogens, and that the identity of those exposed and the type of exposure should be formally recorded and made accessible, as required, in the future.

Lessons

1. Screening for carcinogens by short-term and animal tests will help to reduce the risks, but will not eliminate all dangers from the workplace. Epidemiological surveillance and record linkage, now available on a national basis, should be utilized to detect risks in those exposed to known or suspect carcinogens.
2. In the case of exposure to known carcinogens, a monitoring system should be established to provide ongoing protection of the individual at risk (e.g. radiation workers). Exposure records should be maintained in order that compensation can be provided where cancer develops, despite precautions taken, and in order that new standards may be developed, if necessary.
3. Epidemiological surveillance of those exposed to suspect carcinogens can be designed to detect increased incidence of disease following exposure to a substance for which evidence on its carcinogenicity has not been precisely obtained.
4. The basic requirement for utilization of the existing surveillance systems is that full personal details, including Social Insurance Number or other unique personal identifier, be provided.

5. The continued existence of provincial cancer registries, such as the Ontario Cancer Registry, must be ensured in order that full cancer surveillance can be maintained.
6. Existing industrial practice, in well-managed plants, of maintaining exposure records should be encouraged and developed in order that complete and detailed records are kept of those exposed to known and suspect carcinogens, and are available for study and record linkage purposes.

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APPENDIX A

Case History — Ionizing Radiation

Radiation hazards have been under scrutiny for over 80 years. This very extensive experience with a physical carcinogenic agent has led to the development of concepts which are applicable to other carcinogens. The most important of these is the non-threshold concept, which indicates that some degree of risk is associated with any exposure to ionizing radiation. This concept leads to an emphasis on estimation of risk, rather than on determination of a 'threshold dose'.

Awareness of the long-term effects of radiation exposure led to the development of an approach to radiation protection designed to prevent industrial injury in advance, instead of waiting to apply a remedy if overt harm developed. This system of dose limitation has been based on the concept of 'maximum permissible' radiation exposure.¹ The non-threshold concept implies that the 'maximum permissible' dose cannot be regarded as a safe (no effect) dose, but only as a basis for administrative control of radiation exposure. A regulatory limit of this type involves two very different kinds of activity. One is the quantitative estimation of risk. The other involves making judgements about the acceptability of risk. The latter must include a consideration of tradeoffs between benefits and hazards. Only the first of these can be regarded, at present, as an empirical, scientific activity.^{1,2,3}

Brief Historical Perspective

Ionizing radiation (including X- and gamma-rays, electrons, alpha particles and neutrons, but not radio waves, microwaves, infrared, visible or ultra-violet radiation) is often looked upon as an agent which has only recently appeared in the environment. This is not the case: there are several natural sources of 'background' radiation exposure, including terrestrial radiation from naturally-occurring radioactive elements in soil and rock, cosmic radiation, and radiation from radioactive elements in our bodies. However, occupational exposure to ionizing radiation only became of significance following the discovery of X-rays in 1895 and of radioactivity in 1896. These discoveries led quickly to a variety of applications; for example, the remarkable penetrating power of X-rays had already been exploited by Roentgen in late 1895, to make an X-ray photograph of his wife's hand. The fact that ionizing radiation can damage living tissue also became apparent very quickly; hair loss following X-ray photography was reported four months after Roentgen's announcement.⁴

The best documented early group of radiation injuries are those of the radium dial painters in New Jersey.⁵ Luminous paint production and its applications were introduced into North America about 1913; signs of radiation injury were recognized about 1923 and the first published reports appeared in 1925. The luminous watch-dial painters had inhaled or swallowed radium which, being chemically similar to calcium, was incorporated into bone. These workers were thus chronically exposed to radiation. At high levels of exposure (well above 100 rads per year), acute destruction of bone and bone marrow resulted in death within a few years. At lower exposure levels, the bone lesions were less acute: the affected workers lived longer, some long enough to develop bone cancers. Those dial painters who received an estimated average total skeletal dose of approximately 10^4 rads (100 Gy)

showed the highest incidence of tumours; more than 40 per cent of those individuals developed bone sarcomas.⁶ There were very few cases of leukemia, although there is good evidence (especially from the survivors of the atomic bomb explosions at Hiroshima and Nagasaki) that irradiation of the bone marrow can lead to an increased incidence of leukemia.²

The experience of early workers in radiation also revealed that repeated doses of radiation that are too small to produce any immediate reaction may eventually have an effect. For example, the hands of many pioneer radiologists were exposed repeatedly to radiation of low penetrating power from low-voltage X-ray machines, because of the practise of checking X-ray tube operation by using the hand as the test object. After a time, they gradually developed dry cracked skin, brittle fingernails and poorly healing ulcers that, years later, became cancerous.⁷

Sources of Radiation

The major sources of ionizing radiation to which the general population is exposed are natural background radiation, and medical applications of radiation (Table 1). For a given person, the dose from natural background varies with altitude and geographic location, as well as living habits. Occupational exposures may exceed background by severalfold.²

Table 1

Annual Dose Rates From Some Important Sources of Radiation Exposure in the U.S.

<i>Source</i>	<i>No. Exposed</i>	<i>Average dose rate to exposed group (m rem/yr.)</i>
Natural background:		
Cosmic radiation	220 × 10 ⁶	28
Terrestrial radiation	220 × 10 ⁶	26
Internal sources	220 × 10 ⁶	24 (BM)*
Medical X-rays:		
Medical diagnosis	105 × 10 ⁶ /yr	103 (BM)
Medical personnel	195,000	300 - 350
Dental diagnosis	105 × 10 ⁶ /yr	3 (BM)
Dental personnel	171,000	50 - 125
Radiopharmaceuticals:		
Medical diagnosis	10 × 10 ⁶ /yr	300 (BM)
Medical personnel	100,000	260 - 350
Nuclear Industry:		
Nuclear power plants	67,000	400
Industrial radiography	11,250	320
Research Activities:		
X-ray diffraction units	10,000 - 20,000	?
Airlines:		
Crew members	40,000	160

*BM = dose to bone marrow

Taken from: Reference 2, pp. 84-87 (This report, familiarly known as BEIR III, contains a wealth of detailed information).

Radiation Dose Measurement

Extremely sensitive methods are available for the measurement of radiation dose. Major difficulties in the measurement of dose usually arise only when radiation doses must be estimated after the fact. For example, for the Japanese atomic bomb survivors, great efforts have been made to determine the dose-distance relationships of the bombs, to locate the site of exposure of each person in the city at the time of the bombing, and to determine the degree of shielding by buildings or terrain that may have reduced radiation exposure.

Units of radiation are the rad (0.01 joule/kg of absorbed dose) and the rem (absorbed dose multiplied by a correction factor to allow for differences between radiations in their biological effects); these older units are now being replaced by two new units, the gray (1 Gy = 100 rads = 1 J/kg) and the sievert (1 Sv = 100 rems). Very low levels of exposure are usually expressed in millirems per year (1 rem = 1000 mrem).

Radiation Biology

The relationship of radiation biology to radiation carcinogenesis is similar to that of pharmacology to chemical carcinogenesis. However, ionizing radiation is unique, in that the energy it deposits in biological material is distributed in discrete packets, essentially at random, along the tracks of charged particles set in motion in the material as a consequence of transfer of energy from the radiation to the material. Because of the penetrating power of many ionizing radiations, and the random nature of the deposition of energy, no component of the irradiated material is spared.

Theoretical considerations, and cellular and animal data, suggest a model for the dependence of biological effects on dose at relatively low doses, well below 100 rads, where the cell-killing effects of ionizing radiation are negligible. The model is a linear quadratic dose response curve^{2,3}:

$$E = a_0 + a_1D + a_2D^2$$

where D is the radiation dose, E is the incidence of effects (e.g. cancer) at dose D , a_0 is the control, or spontaneous rate of the effect under study, and a_1 and a_2 are positive-valued parameters that depend on a number of factors related to the nature of the ionizing radiation and of the biological effect involved. This functional form can be viewed as a basically linear function ($a_0 + a_1D$) with a modification that allows the curve to express upward (positive) curvature (a_2D^2).

The essential features of the linear-quadratic model are³:

1. Ionizing radiation produces elementary lesions, in numbers proportional to the absorbed dose, within a small sensitive site in the biological material.
2. If two lesions occur close enough together in space, they can interact to produce a biological effect. The probability that two lesions will occur in the same critical volume is determined by the dose.

3. For sparsely-ionizing radiation (such as high energy electrons set in motion by X- or gamma rays), each of these interacting lesions will be produced independently of each other (that is, by independent charged particles), thus producing a dose-response curve proportional to dose squared.
4. For more densely-ionizing radiation (such as alpha radiation, the recoil protons produced by neutrons, or low-energy electrons), both of the interacting sublesions can be produced by one particle and the dose-response curve will be linear (directly proportional to dose).
5. Some forms of radiation damage in biological material are repairable; thus two lesions that do not occur close enough together in time may not interact to produce a biological effect. The probability that two lesions occur within a given time interval is determined by the dose-rate.

Thus, for very low doses and low dose rates, for either sparsely or densely-ionizing radiations, the dose response curve should approach linearity.

The nature of the dose-response curve is of great importance in risk estimation, since extrapolation from high dose levels to low levels is required. If the linear-quadratic model is correct, it is likely that effects at low dose levels, at least for sparsely-ionizing radiation, will be overestimated on the basis of a linear extrapolation of data obtained at high doses and dose rates.

The validity of the linear-quadratic model, relative to a more conservative linear model, as a basis for risk estimation remains controversial; for a thorough discussion of the issue, see the BEIR III report.²

Types of Cancer Induced

Cancers induced by ionizing radiation are indistinguishable from those occurring naturally; hence, their existence can be inferred only on the basis of a statistical excess above natural incidence. This means that the cancer of any given person cannot be attributed with certainty to radiation, as opposed to some other cause.

Cancer may be induced by ionizing radiation in nearly all the tissues of the human body, although tissues and organs vary considerably in their sensitivity. Leukemia stands out because of the relative ease of its induction by radiation, and its short latent period (2-4 yrs.). When the total risk of radiation-induced cancers is considered, it is clear that the risk of other cancers exceeds that of leukemia.

The major radiation-induced cancers are summarized in Table 2, taken from the BEIR III report.²

Table 2

Major Radiation-induced Cancers

<i>Site or type</i>	<i>Spontaneous incidence</i>	<i>Relative sensitivity to radiation induction</i>
Female breast	Very high	High
Thyroid	Low	Very high (esp. for females)
Lung (bronchus)	Very high	Moderate
Leukemia	Moderate	Very high
Alimentary tract	High	Moderate to low

Latent Period

The time elapsing between irradiation and the appearance of a detectable neoplasm is characteristically long; that is, years or even decades.² The excess risk of leukemia appears within a few years after radiation exposure and largely disappears within 30 years after exposure. For other cancers, latent periods appear to be longer; they seldom appear before 10 years after radiation exposure and may continue to appear for 30 years or more after radiation exposure. Because of the very long latent periods which may separate exposure to radiation and the development of detectable effects in man, the true health risk of radiation exposure can be assessed only with extremely long followup (30 years or more) of the populations under study. It is usually necessary to make some assumptions about the way in which further cases are likely to appear in later years. Examples of two models for projecting the effect of radiation exposure at a particular dose level are the 'absolute-risk' model, and the 'relative-risk' model. In the former, absolute risk is defined as the number of excess cancer cases per unit of population per unit of time and per unit of radiation dose, and, although it may depend on age at exposure, it is assumed not to depend otherwise on age at the time of observation for assessment of risk. In the second model, excess cancer risk for the interval after the latent period is expressed as a multiple of the natural age-specific cancer risk for that population. The chief difference between the two models is that the latter involves the assumption that the absolute risk of radiation-induced cancer varies by age at observation and is proportional to the risk of spontaneous development of cancer in the population. For either model, the total risk to an irradiated population for its entire life span can only be estimated by making an assumption about how long the risk will remain increased. Reasonable estimates can be made for leukemia and for bone cancer arising from radium-224 exposure, but for virtually all other radiogenic cancers, excess risk has not decreased 30 years or more after exposure, and final risk estimates cannot be made.

Effect of Age

The most important factor influencing the risk of spontaneous cancer is age. The available data show that age at exposure to ionizing radiation has an

important influence on its carcinogenic effect. If the relative-risk model (see above) applies, then the age of the exposed groups at the time of observation also becomes important. However, the influence of age is not uniform in human carcinogenesis.² For example, the clearest evidence of a very high risk in those irradiated in the first years of life is provided by the age-specific data for leukemia induction for atomic-bomb survivors. The excess risk of breast cancer appears to be highest for women exposed in the second decade of life, when major hormonal changes are taking place. For lung cancer, there is little evidence of increased risk before the age of 35, regardless of the age at exposure, but the risk at later ages increases steeply, as does the risk in the general population. For the major solid tumours, whatever the age differential in susceptibility, a differential in the length of the minimal latent period seems quite well established; persons irradiated at higher ages in general develop cancer sooner than those irradiated at lower ages. An association between prenatal exposure to ionizing radiation and an increased risk of developing malignancy during childhood has also been established, but there remains some question as to the extent to which this represents a causal relationship.²

Other Variables

Various host or environmental factors may interact with radiation to affect cancer incidence in different tissues. A few principles are now evident.² For example, sensitivity to cancer induction is not proportional to the rate of division of stem cells; if it were, the small intestine should be as sensitive as the bone marrow, and it is not. Nor is sensitivity to radiation necessarily related to the influence of hormones. The female breast and the thyroid are quite sensitive to radiation, but the uterus and prostate are not.

Some groups in the general population appear to be at increased risk of induction of cancer by radiation. For example, cigarette smoking appears to lead to greater excess risk of lung cancer from radiation exposure, when smokers and non-smokers are compared. Smoking appears to shorten the latent period, but more information is needed to settle the question whether exposure to radiation simply adds to the effect of cigarette-smoking, or whether the effects are greater than additive when both are present.

There is increasing recognition that there are human genotypes that confer both increased cancer risk and abnormal sensitivity to carcinogenic agents, including ionizing radiation. To the extent that substantial population subsets can be identified in the future as being at particularly greater risk of radiation carcinogenesis, their risk merits separate consideration. However, current evidence would seem to be against large differences in sensitivity to ionizing radiation within the population.⁶

Risk Estimation

A clear-cut increase in cancer incidence and mortality with increasing radiation dose has been demonstrated for many types of cancer in human populations, as well as in laboratory animals. However, the quantitative estimation of the carcinogenic risk of radiation is subject to numerous uncertainties. The greatest of these concerns is the shape of the dose-response curve, especially at low doses. Estimates of risk at low doses depend more on what is assumed about the mathematical form of the dose-response relationship than on the data themselves.⁶ The uncertainties involved in

the estimation of carcinogenic risk are such that it is not clear whether or not dose rates of gamma or X-rays of about 100 mrad/yr. (i.e., equivalent to natural background radiation) or less are detrimental to man. Any carcinogenic effects at these dose rates would be masked by environmental or other factors that produce the same types of health effects as does ionizing radiation. Indeed, in studies of either animal or human populations, the shape of a dose-response relationship may be practically impossible to ascertain statistically. This is because the sample sizes required to estimate or test a small absolute cancer excess are extremely large, e.g. of the order of 100,000 exposed and 100,000 control subjects are required to test the cancer excess adequately for a dose of 10 rads.² Because of this uncertainty, there has been no general agreement over the choice of a mathematical model; the linear and quadratic models can lead to widely diverging estimates at low dose levels, with the linear-quadratic model yielding intermediate values. As discussed above, the linear model provides a conservative approach; although it may overestimate risks at very low dose levels, it is unlikely to underestimate them.⁹

Other uncertainties involved in risk estimation pertain to the length of the latent period, the biological effectiveness of fast neutrons and alpha radiation relative to gamma and X-radiation, the period during which the radiation risk is expressed, the model used in projecting risk beyond the period of observation, the effect of dose rates or dose fractionation, the influence of differences in the natural incidence of specific forms of cancer, and others.

The chief sources of human data are the populations exposed to whole-body irradiation at Hiroshima and Nagasaki, patients with ankylosing spondylitis and other patients who were exposed to partial-body radiation therapeutically, and various occupationally-exposed populations, such as uranium miners and radium-dial painters. Most epidemiologic data do not systematically cover the range of low to moderate doses for which the Japanese data appear to be fairly strong. Analysis in terms of dose-response therefore relies rather heavily on the Japanese atomic-bomb survivor data.

There are some problems in the use of epidemiological studies as the principal source of information about the carcinogenic effects of ionizing radiation on human populations.² The main problems are:

1. Generally, the group has been exposed to radiation because of some particular characteristic, and thus may not be representative of the population as a whole.
2. Most such studies are retrospective. That is, exposure to radiation occurred in the past, and the exact dose delivered to individuals or to a group may not be known.
3. Very long latent periods may separate exposure to radiation and the development of detectable effects in man. This is a problem especially if the latent period is influenced by demographic variables such as age at exposure.

Although risk estimation at low dose levels involves the various sources of uncertainty outlined above, some numerical risk estimates can be given. For doses of sparsely-ionizing radiation of the order of 50 rads, the absolute lifetime risk of mortality from cancer is about 10^{-4} per person per rad.

for young adults, averaged for both sexes.⁶ If tumour incidence, rather than mortality, is used, the estimates are somewhat higher. For continuous lifetime exposure to 1 rad per year, on the basis of the linear-quadratic dose response model, the increased risk expressed as per cent of the normal incidence of cancer in males is about two per cent – six per cent, depending on the projection model used (absolute-risk or relative-risk).^{2,10} Risk for females is substantially higher than that for males, due primarily to the relative importance of radiation-induced thyroid and breast cancer.²

Risk Assessment

The elements of risk assessment are three-fold: risk identification, risk estimation, and risk evaluation.¹¹ Identification of ionizing radiations as carcinogenic agents is well-established; all of the criteria of causation described by Bradford Hill¹² are satisfied. Quantitative risk estimation is possible, as is outlined in the previous section. It is the third element of risk assessment, risk evaluation, that poses major problems in terms of quantitative analysis.

If the concept of a non-threshold dose-response function is accepted, it follows that any risk associated with man-made radiation must be compensated for by an appropriate benefit. There is no general agreement about how the quantitative comparison of risks and benefits should be made. Early approaches to the regulation of radiation exposure were based, at least partly, on the concept of 'absence of serious harm'.⁶ Over the past 25 years, this concept has been replaced by the concept of 'acceptable level of risk'. One quantitative approach to the definition of an acceptable level of risk is to utilize the concept of 'comparative risk', such that risks from sources of hazard other than radiation play a role in determining acceptability of risk.⁶ However, perceptions of risk must also be included in judgements about the acceptability of estimates of comparative risk.⁶ Empirical work has shown that a variety of factors can strongly influence attitudes toward risk.^{13,14} For example, people usually consider voluntary risks to be much more acceptable than involuntary ones. They tend to trust familiar, concrete experiences more than abstract statistics, and to overestimate the magnitude of risk associated with dramatic and sensational causes of death relative to the risk associated with potentially lethal events that are also common in nonfatal forms.¹⁵ Thus, judgements of the acceptability of comparative risk (such as the risks associated with exposure to ionizing radiation relative to other potentially hazardous activities) are open to a number of biases. There is no general agreement about how such biases might be taken into account in policy-making.

Other approaches to the regulation of radiation exposure have also been considered; again, no consensus has emerged. An example is the 'de minimus' concept, that a specified increase in hazard level might be considered acceptable in order to achieve compensatory benefit, provided that the added hazard level remains small in comparison with the variation that already exists. For radiation exposure, the de minimus level might be defined as some specified proportion of the standard deviation in population exposure to natural background radiation.¹ Natural radiation levels are relatively well-known: cosmic radiation levels vary with altitude, by about two-fold from sea level to 1500 meters (5000 feet). Terrestrial radiation varies considerably also: in some heavily-populated parts of Yangjiang County,

Guangdong Province, China, the terrestrial radiation level is about three times that in neighboring areas.¹⁶ In some populated locations, such as the area of monazite sand in Kerala, India, the terrestrial radiation levels are much higher.¹⁷

For any arbitrarily chosen level of risk for which the degree of harm is presumed to be 'acceptable' relative to the expected benefits, there is the concern that those who undertake activities in order to receive benefits are not always those who must take the risks. An approach which pays some attention to this aspect of risk evaluation is the ALARA principle: as low as reasonably achievable in all areas of exposure to ionizing radiations, economic and social factors being taken into account.¹⁸ Two factors influence practical applications of this principle¹¹: even very low exposures involve risks that require compensating benefits, and the cost of control measures needs to be offset by benefits of reduced risk. It cannot be assumed that conservative estimates of risk do not involve any concomitant increase in costs. For example, penetrating high energy gamma radiation is attenuated by shielding materials such as lead or concrete according to a negative exponential rather than a linear relationship.¹⁹ This means that the thickness (and cost) for the shielding materials must increase by approximately two-fold for each two-fold reduction in the dose-rate of the emergent radiation, and an infinite thickness is required to achieve a zero dose-rate.

Approaches to the analysis of risks associated with ionizing radiation continue to evolve. Recent revisions of dose estimates at Hiroshima and Nagasaki²⁰ may have some impact on risk estimation. Risk assessment remains a controversial topic, and is being studied intensively by a series of national² and international²¹ committees. Present policy in Canada for penetrating high energy X- or gamma radiation²² is based on what may be regarded as a compromise approach involving the ALARA principle, the 'de minimus' concept, and the concept of a 'permissible' level of radiation exposure. Reasons must now be given why any exposure of the general public to man-made radiation exceeding 5 millirem per year should be permitted. This low level of exposure (corresponding to about five per cent of the background level from natural sources) has become, in effect, the current guideline concerning exposure to penetrating high energy ionizing radiation for a member of the general public. Departures from this level of exposure are based on the ALARA principle, in that they must be justified as being as low as reasonably achievable, economic and social factors being taken into account. It should be emphasized that this policy for penetrating high energy radiation is *not* based on the concept of 'comparative risk'.⁶ The risks associated with ionizing radiation are, at present, perceived to be much less acceptable than those associated with a variety of other potentially hazardous activities,²³ even for equivalent levels of estimated 'objective' risk.

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APPENDIX B

Case History — Vinyl Chloride

One Model for a Human Chemical Carcinogen

The model of vinyl chloride induced chronic disease, in particular liver cancer, is both interesting and informative for several reasons:¹

- 1) the relatively short and well-defined time period for its use,
- 2) the characteristic end points for health — chronic bone and soft tissue changes (acro-osteolysis) and angiosarcoma of the liver,
- 3) a readily identifiable exposure pattern,
- 4) a great interest in the problem by many segments of the population,
- 5) the ready availability of animal models, and
- 6) a fairly easy and acceptable way to handle the problem in the work-place.

A. Brief Historical Perspective

Vinyl chloride (VC) is one of the major intermediates in the commercial production of one of the most important plastics, polyvinyl chloride (PVC). VC is a gas at ordinary room temperature and pressure but is easily compressed to form a liquid. It is readily polymerized to form PVCs.

The world productive capacity has increased very significantly from 1950 to the 1970s. For example, the capacity increased in Western Europe by about 75 fold from 1950 to 1972 and in the USA by about one-and-a-half fold from 1972 to 1975.

VC was shown to be toxic to animals in 1960² and found to induce vascular disease with bone destruction (acro-osteolysis) in 1963 in Romania.³ It was found to induce cancer in several sites in 1970,⁴ and angiosarcoma of the liver in humans in 1974.⁵ The human pathological picture was largely reproduced in experimental animals in respect to chronic liver disease including liver cancer.⁶ Thus, within less than a 15-year period, the major acute and chronic disease patterns induced by exposure to VC were described.

The total work population in the USA concerned in some way with VC, past and present, has been estimated at about 20,000.¹ However, there is some evidence that a much larger population may have some hazardous exposure because of:

- 1) significant loss of VC to the atmosphere at selected sites with subsequent atmospheric transport,
- 2) proximity to VC and PVC production areas,
- 3) consumption of food products containing leakable amounts of unreacted VC from PVC-packaged materials, and
- 4) ingestion of water containing unreacted VC leaked from PVC pipes.⁷

How great the risk is in such groups is not known.

B. Characteristics

a) Metabolic Activation and Reaction With Cellular Constituents

There is now clear-cut evidence that VC per se is not the likely carcinogen but rather a chemically reactive derivative generated enzymatically in the liver (and possibly elsewhere).⁸ This would place VC in with the majority of chemical carcinogens that require metabolic conversion to active compounds that in turn can react with many components in the tissues including DNA. In several test systems *in vitro*, VC has been found to be mutagenic, especially in the presence of purified liver microsomes capable of carrying out some type of metabolic conversion. The exact chemical form (or forms) that is the 'ultimate carcinogen' is not known. Chloroethylene oxide, the epoxide of VC, ($\text{H}_2\text{C}-\underset{\text{O}}{\underset{\text{||}}{\text{CH}}}-\text{CH}_2\text{Cl}$) is considered to be a likely candidate.

Thus, in respect to metabolic activation, mutagenic activity after activation and interactions with cellular constituents, VC is quite a typical chemical carcinogen.

b) Exposure Pattern

It is already evident that exposure to VC need not be continuous up until clinical cancer appears.⁹ In three of the first cases reported, initial exposure (as a 'helper' cleaning out the interiors of polymerization vats) of only an average of 5.3 months resulted in liver cancer 22 years later, while in four cases, the exposure averaged 34.5 months and cancer appeared 14.5 years later.

The available evidence indicates that even removal of the person from further exposure to VC may nevertheless not prevent cancer appearance years later. Thus, certain tissue changes appear to be fairly irreversible. In the first 13 patients in the USA, the total exposure in VC work varied from 13 to 29 years. This, coupled with the current understanding of the pathology and pathogenesis,¹⁰ makes it almost certain that VC-induced angiosarcoma, like most other malignant neoplasms of many sites, develops as a multistep process with the probable occurrence of non-neoplastic or non-cancerous changes some considerable time before cancer appears. This process could well take from 15 to 25 years or more, depending upon the intensity and duration of exposure and other unknown factors.

c) Initiation — Promotion

The available data on VC carcinogenesis in humans, although far from extensive, nevertheless are consistent with the data from other human exposures to other carcinogens and from extensive animal experience in indicating that the first step or steps in the carcinogenic process might well be irreversible. This would fit well with the concept that initiation of the carcinogenic process begins as a few steps generating some change that can persist for a long time. This is most easily interpreted as a mutation-like event, although other possible mechanisms of inducing an irreversible change in the behaviour of a cell have not been ruled out.

The identity of any possible promoting agents, other than the carcinogen itself is quite unknown.

d) Organ and Cell Specificity

The appearance of a rare form of cancer of the liver, angiosarcoma, with exposure to VC has no readily apparent explanation. This form of liver cancer is seen with several different carcinogens in experimental animals, in addition to VC. Dimethylnitrosamine, dimethylhydrazine and urethane are among the carcinogens that induce this form of liver cancer in animals. In humans, thorotrast, the particulate form of the radioactive compound thorium dioxide, also induces a similar form of liver cancer after many years.

One possible explanation was suggested recently.¹¹ Dimethylhydrazine (DMH) was shown to react with both liver parenchymal cells and vascular endothelium but the repair of the damaged DNA was found to be much slower in the latter cells. DMH under some conditions induces mostly angiosarcoma.

Another possible explanation may relate to the general effects of VC on blood vessels including both fingers and liver. The initial damage to cells by VC could be relatively non-specific in the liver. However, the promoting action of VC could be much more vigorous on the blood vessels since these seem to be damaged generally by VC. Thus, the specificity could reside in the post-initiation events rather than in those related to initiation.

e) Threshold and Dose Response

The question of threshold may be critical to our eventual control of cancer. Are there safe levels of exposure?

There are some data indicating that there is a rough correlation between degree of exposure to VC and the duration of the period taken to develop clinically evident cancer. However, the data are not many and throw no light upon the question of the existence of a threshold for carcinogenicity.

C. Control

This is an excellent example of a situation where vigorous action on the part of industry and the authorities has led to rapid and radical change in the workplace. Whereas, a few years ago, discussions were concerned with whether 50 ppm is a feasible level to strive for, the vigorous insistence by some authorities on a 'zero' level has stimulated many industries to introduce automation to the point where 0.5 ppm is readily attainable in the workplace in at least some countries (e.g. Sweden).

Thus, the attitudes and the technology have rapidly merged to make the workplace in PVC production a much safer environment than was thought possible five years ago. In this respect, the VC model is particularly attractive and deserves widespread acknowledgment.

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APPENDIX C

Case History — Smoking

a) Lung Cancer

In Canada, lung cancer is the most important cancer in men and is rapidly approaching this position in women.^{1,2} Internationally, the highest incidence rates in males are reported from Liverpool in the United Kingdom, the lowest rate from Ibadan in Nigeria.³ It is notable that a moderately low rate is reported from Utah in the United States where a high proportion of the population are Mormons who do not smoke. In females the highest rate is in the Maoris of New Zealand with oriental populations from a number of areas (Bay area of the U.S., Hawaii and Singapore) showing high rates, as well as white females in the Bay area and Hawaii. Canadian registries occupy an intermediate position in both sexes.

A useful way of presenting rates for comparative purposes is to cumulate incidence. If you cumulate rates to age 75 you achieve an approximation to a lifetime incidence of the disease in question, excluding other competing causes of death. In Canada, currently the cumulative incidence for lung cancer to age 75 approximates to six per cent for males and is just over one per cent for females. There are substantial variations in these rates internationally and in the changes that have occurred (Table 1). For example, in Liverpool, cumulative incidence has shown a 14 per cent increase to 11.6 per cent, in Connecticut it increased 24 per cent to 6.9 per cent, in Saskatchewan 64 per cent to 4.6 per cent, and in the Singapore Chinese over 400 per cent to 7.6 per cent, though the earlier figures were based on rates in 1950-61. In females similar, if not larger, changes have occurred. Thus, in Saskatchewan there has been over a 100 per cent increase to 0.8 per cent.

Many years ago the changes that were occurring in mortality from lung cancer were interpreted as showing the influence of an environmental factor.⁴ Changes are still continuing as is shown with the continued upward trend in mortality from lung cancer in Canada¹ though the rate of increase is less now in males than in females.² The marked international variation confirms the importance of environmental factors as do the changes that have occurred in the rates of disease in groups of migrants. Those who migrate from Britain to Canada, Australia and South Africa tend to end up with rates intermediate between those they might have been expected to have encountered if they had remained in Britain and those that prevailed in the host country, even when account is taken of differences in smoking intensity.^{5,7} The older they were when they migrated, the nearer their rates corresponded to those of Britain. This would seem to suggest that the British were carrying with them a factor related to background exposure to possible causative factors when young, such as virus infections of the respiratory tract or maybe air pollution. Such increased risk seems unlikely to be of genetic origin, even though some studies have suggested familial associations of lung cancer.⁸ In some countries there has been an indication, particularly in males, of a down turn in mortality from lung cancer at certain ages.^{9,10} In Canada, we are just beginning to see such an effect in males between the ages of 40 and 49 though with a suggestion of a reduction in the rate of increase in lung cancer at all ages, except possibly those older than 70.² In females there is, however, no indication of any slow down in the rates of increase of lung cancer at any age.

In view of the fact that the increases that were seen in mortality in every country appeared to follow the increase in tobacco usage, particularly cigarette consumption, after an appropriate latent interval, specific investigations of tobacco use and lung cancer were performed.^{11,12} Initially conducted by comparing the tobacco usage experience in cases with lung cancer and suitable controls (the case-control approach), a number of different cohort (longitudinal) studies were performed in which groups had their tobacco experience identified, and their subsequent incidence and mortality from lung cancer, other cancers and other diseases monitored.^{13,14} The long-term study of British doctors encompasses a 20-year follow-up period of an occupational group in which the effect of tobacco consumption could be efficiently determined without confounding from other occupational causes.¹⁵ The study confirmed the increased risk of death from lung cancer with any tobacco use but most specifically usage of cigarettes and with a strong dose-response relationship between different cigarette consumption categories (Table 2). The very strong dose-response relationship and the high relative risks at high consumption levels point strongly to a causal association. The study also provided additional confirmatory evidence of a causal association by documenting reduced risk following cessation of cigarette smoking (Table 3). When expressed as a ratio of rates compared to non-smokers, continuing cigarette smokers had a ratio of 15.8:1, ex-cigarette smokers one of 2:1 after 15 years, or as 11 per cent of the risk in continuing cigarette smokers. However, a number of cautions are necessary in interpreting these data. First, it must be borne in mind that the comparisons are with those who continue to smoke or do not smoke. As continuing smokers age they increase their risk. Those who stop smoking appear to have acquired a certain degree of risk at the time they stop and this degree of risk persists, though in comparison with continuing smokers, it becomes less. In other words, cigarette consumption for a period results in cumulating a certain order of risk which then persists at that level even if exposure then ceases. The second caution relates to the fact that those who give up cigarette smoking are a self-selected group. An intervention study conducted among British civil servants has so far suggested no effect on overall mortality in a group where a majority ceased smoking compared to a group in which a minority ceased smoking.¹⁶ Indeed, a recent analysis claims that, although mortality has fallen substantially from lung cancer and heart disease in physicians in Britain who have ceased smoking, this may have been partially offset by increases in mortality from other causes related to stress.¹⁷

One factor which might partially explain a deceleration in the increase in lung cancer mortality and incidence in various countries, is the shift that has occurred almost universally, except possibly in developing countries, to filter cigarettes burning tobacco with lower tar production.¹⁸ As those who are currently dying from lung cancer are largely those who commenced smoking with non-filter cigarettes many years ago, it is difficult to dissect fully the effects of the earlier consumption from the more recent, possibly less hazardous consumption. In addition, there is evidence that those who shift to filter and lower tar brands tend to increase their consumption to compensate for the decreased nicotine^{18,19} so that although comparisons have

been made within cigarette smoking categories, the 20 or more filter cigarette smoker may have been a less than 20 non-filter cigarette smoker. Bearing these caveats in mind, however, in an American Health Foundation study the relative risk for non-filter smokers compared to long-term filter smokers was, after adjusting for various factors, estimated to be 1.3 for males and 1.4 for females.²⁰

Lung cancer in women has not been subjected to the same intensity of study as for men. However, recently a follow-up of female British doctors has suggested that the relationship between smoking risk and lung cancer is similar to that of men at similar dose levels of cigarette consumption.²¹ Marshall and his colleagues have also shown that women have similar smoking habits as men once they reach the 'addictive' stage of 20 or more cigarettes daily.²² It seems likely, therefore, that the lower lung cancer rate in women is only a reflection of lower smoking levels overall, not a difference in biological susceptibility to the carcinogens in tobacco.

Currently in Canada, it would seem that cigarette smoking accounts for approximately 80 percent of the lung cancer in males and nearly 60 per cent in females.² This fraction, the attributable risk, is increasing in females though remaining approximately stable in males. It is important when considering such figures, however, to bear in mind that the attributable risk when a number of different factors have been included, can easily amount to more than 100 per cent. However, the concept implies that if you are able to remove a factor from the environment, then theoretically that amount of cancer currently occurring could be prevented.

A large number of different occupational factors have now been identified as associated with lung cancer.²³ Thus, exposure to asbestos in insulation workers, miners and millers, textile workers, shipyard workers, construction, and particularly demolition workers, is well recognized as increasing the risk of lung cancer. Exposure to polycyclic aromatic hydrocarbons is believed responsible for the increased risk in gas workers, coke oven workers, various groups of roofing workers and foundry workers. Exposure to radioisotopes, particularly to radon daughters, is recognized as causing lung cancer among various groups of miners,²⁴ especially uranium and fluorspar miners in Canada and the Colorado plateau in the United States, while the hematite workers in Great Britain are believed to have an increased risk, at least partially because of radiation exposure, as may many hard rock miners the world over. Nickel is now well recognized as a respiratory carcinogen having been first identified in South Wales,²⁵ Norway,²⁶ and Canada.²⁷

Asbestos provides an example of the interaction of tobacco with an occupational factor. A cohort of 17,800 asbestos insulation workers was established by Selikoff on January 1, 1967. Up to December 31, 1974,²⁸ the ratio of observed to expected deaths from lung cancer was 3.2 for those with less than 20 years from first exposure and to 4.9 for those with more than 20 years from onset of exposure. A questionnaire was administered to this cohort on cigarette smoking and data on deaths up to December 31, 1972 have been analysed according to the smoking habits ascertained in the questionnaire. This indicated little increase in risk for those who had never smoked cigarettes or smoked pipes or cigars only, but nearly a six-fold

risk for those who smoked cigarettes as well as those whose smoking habits were unknown. The latter group are believed to be largely a group of cigarette smokers.

As has been pointed out by Saracci²⁹ the data are compatible with an increased risk from asbestos exposure as well as an increased risk from cigarette smoking. This has now been confirmed by an updated analysis.³⁰ Selikoff has related the observed numbers of lung cancer to those expected on the basis of cigarette smoking specific rates in the long term study of cigarette smoking conducted by Hammond of the American Cancer Society. This results in a ratio of observed to expected for asbestos exposure approximating to five when one uses non-smoking individuals as the basis for expectation.

These data are compatible with those which might have been expected as is indicated in Table 4. Thus, the risk ratios for asbestos workers in general when compared to the general population approximate to five and to six when one compares cigarette smoking asbestos workers with the general population. However, when you calculate from Selikoff's published data the ratio for cigarette smoking asbestos workers compared to non-cigarette smoking asbestos workers, it reaches approximately 20 which is not incompatible with the ratios for cigarette smokers in general, or cigarette smokers who smoke 25 or more from the study of Doll and Peto.¹³ As all the evidence appears to point to an interaction between cigarette smoking and asbestos exposure with a multiplicative interaction of the rates,²⁹ one could anticipate that the risk ratio for cigarette smoking asbestos workers compared to a non-cigarette smoking non-asbestos exposed general population group would approximate to 100. Selikoff's data seem to confirm this very well.³⁰

In conclusion, in lung cancer we are dealing with one of the most clearly identified carcinogenic risk factors for any cancer in man, namely cigarette smoking. Although other factors are important and justify attention, such as occupational exposure and air pollution, a major reduction in lung cancer incidence and mortality is only going to be possible by a substantial shift in population exposure to cigarette smoking. In Canada, a reduction in smoking in males gives rise to cautious optimism³¹ (Table 5) but the failure of this reduction to occur in females, particularly younger females, suggests it may be many years before the current increase in rates of lung cancer in women are brought to a halt. However, gains are being made: smoking is being banned in public places, non-smoking sections of airplanes, trains, buses are now usually available and regarded as a right in some countries, and a gradual change in the perception by the public of the tolerability of cigarette smoking appears to be occurring. It is thus possible that, in another two or three decades, we will begin to see the effect of a major impact on society's attitude towards smoking, in most technically advanced countries, in a reduction in both the incidence and mortality from lung cancer in both sexes.

b) Bladder Cancer

Bladder cancer has been known to be associated with cigarette smoking for some years,^{12, 14} though the earlier reports of the follow-up of British doctors³² cast some doubt on this. The more recent report confirms an

increase in the death rate from bladder cancer in smokers.¹⁵ In a case control study of bladder cancer in Canada,¹⁶ a strong association was confirmed in both males and females (Table 6). The population attributable risk for cigarette smoking was 61 per cent for males and 26 per cent for females. In this study an apparently reduced risk for filter cigarette smoking was found, and a risk for pipe smoking after controlling for cigarette smoking. There was, however, no evidence of interaction between the occupational causes of bladder cancer (attributable risk for high risk industries of eight per cent) and cigarette smoking in contradistinction to the evidence for lung cancer.

c) Laryngeal Cancer

Laryngeal cancer is well recognized as associated with cigarette smoking, alcohol consumption and a number of different occupational exposures.^{14, 15} In a case-control study in Ontario, these associations have been confirmed but no evidence has been found for a reduced risk with smoking filter cigarettes.¹⁶ However, there does seem to be an interaction between cigarette smoking and occupational exposures, especially asbestos.

d) Oral and Pharyngeal Cancer

These sites are well recognized as associated with tobacco and alcohol with marked synergy between them.¹⁷ However, the authors are not aware of any reported interaction between smoking and occupation exposures.

e) Gastro-intestinal Cancer

Alcohol and tobacco act synergistically to increase the risk of oesophageal cancer.¹⁸ Stomach cancer has so far been associated with smoking only in Japan,¹⁹ but this may be an indication of another risk so far unidentified as the risk ratio is low (1.6) and no increased risk has been identified for stomach cancer in the large cohort studies. No association has so far been identified for colon or rectal cancer. Although all of these sites are associated with increased risk from asbestos exposure²⁰ there is no evidence of interaction between occupational exposure and tobacco consumption.

Pancreatic cancer has been increasing in Western countries since the last war, but in the last few years the increase may have come to an end. The association of pancreatic cancer with cigarette smoking is well recognized.⁴¹ By the use of mathematical modelling approaches, Moolgavkar (personal communication, 1980) has calculated that a substantial proportion of pancreatic cancer may be attributable to cigarette consumption, and that much of the increase was due to this cause.

CONCLUSION

There is no question that a substantial and still increasing burden of human cancer is causally associated with tobacco and, particularly, cigarette consumption. Although there has been a recent U.S. publication suggesting an increase in cancer incidence is occurring in some sites not associated with tobacco usage,⁴² it seems very probable that this increase is artifactual resulting from changes in cancer registration procedures rather than the impact of general environmental, and particularly chemical carcinogen exposures as some have claimed. It seems very probable, therefore, that overall cancer incidence and mortality could now be falling in both sexes were it not for cigarette smoking. It can be calculated from Canadian data that the average life expectancy of cigarette smoking males is 7 years less than that of non-smokers. It can also be determined that the lifetime risk of death from cigarette smoking associated cancer in males in Canada approximates to 15 per cent (after correcting for other causes of death) compared to less than three per cent in non-smokers. Most of this difference is due to lung cancer (12 per cent compared to less than two per cent). Nevertheless, the controversy which followed the release of a U.S. NCI-NIOSH document suggesting the possibility that over the next 20 years the proportion of cancer attributable to occupational exposures might increase to as much as 40 percent, indicated that many did not understand the concept of population attributable risk. Thus, in some populations it is possible for 90 per cent of lung cancer to be attributable to cigarette smoking, and also 40 per cent or more to occupational exposures. All this means is that the etiology of lung cancer is multi-factorial, and that at least 30 per cent is caused by the interaction of cigarette smoking and occupational exposure in the same individual, with a multiplicative increase in risk (as in Table 4), but with the implication that prevention of such cases is possible with the control of either cigarette smoking or occupational exposure.

Whether in Canada it is possible to mimic the approach recently adopted in Norway, where only non-smokers are permitted to work in some industries involving asbestos exposure, is debatable. However, it is clear that at least for larynx and lung cancer, control of cigarette smoking will have a much greater impact than attempts to control occupational exposures. What is still not clear is whether cessation of cigarette smoking will reduce the risk of subsequent lung cancer in those already exposed, or whether active prophylaxis⁴³ is the only option. Further research into these issues is urgently required.

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Table 1.

Change in cumulative incidence per 100 to age 75 in incidence of cancer of the lung reported by registries contributing to Volumes I and III of Cancer Incidence in Five Continents:

Registry	Males			Females		
	1959-62	1968-72	% change	1959-62	1968-72	% change
U.K. Liverpool	10.16	11.63	14	1.13	1.81	60
U.K. Birmingham	9.39	10.34	10	0.90	1.43	59
U.K. S. Metr.	9.20	9.54	4	1.22	1.79	47
Finland	8.48	10.07	19	0.50	0.54	8
FRG Hamburg	7.94	8.50	7	0.92	1.12	22
Hawaii Hawaiians	6.67	8.88	33	2.30	3.04	32
U.K. S. West	6.67	8.34	25	0.85	1.33	56
USA Connecticut	5.61	6.94	24	0.79	1.45	84
Hawaii Caucasians	5.42	6.67	23	0.92	2.30	150
Canada Manitoba	5.16	5.63	9	0.74	0.95	28
USA N. York State	4.94	7.03	42	0.55	1.32	140
Yugoslavia Slovenia	3.95	6.10	54	0.53	0.61	15
Canada Alberta	2.98	4.74	59	0.58	0.79	36
Canada Saskatchewan	2.82	4.62	64	0.33	0.83	152
Hawaii Japanese	2.55	3.19	25	0.60	0.89	48
Canada Newfoundland	2.40	4.41	84	0.47	0.35	26
Sweden	2.14	2.85	33	0.49	0.60	22
Colombia Cali	2.07	2.09	1	0.51	0.60	18
Japan Miyagi	2.01	2.46	22	0.66	0.95	44
Jamaica K & St. A.	1.87	2.81	50	0.32	0.64	100
Norway	1.78	2.98	67	0.35	0.55	57
Iceland	1.43	2.01	41	0.49	1.26	157
Singapore Chinese	1.37*	7.62	456	0.32*	2.28	613
Median Change	-	-	25	-	-	48

*Rates derived from 1950-61.

Table 2.

Death rate from lung cancer in males by smoking habits when last asked, British Doctors Study¹³

<i>Tobacco Use Category</i>	<i>Death Rate (Age standardized per 100,000)</i>
Non-smokers	10
Ex-smokers	43
Continuing smokers:	
any tobacco	104
pipe and/or cigar only	58
mixed	82
cigarette smokers only	140
number smoked per day:	
1-14	78
15-24	127
25 or more	251

Table 3.

Mortality from lung cancer in ex-cigarette smokers, British Doctors Study¹³

<i>Compared to:</i>	<i>Years since stopped smoking</i>				
	<i>0</i>	<i>Less than 5</i>	<i>5-9</i>	<i>10-14</i>	<i>15 or more</i>
Non-smokers (Ratio)	15.8	10.7	5.9	4.7	2.0
Continuing Cigarette Smokers (%)	100	68	35	25	11

Table 4.

Risk Ratios for Lung Cancer in Males

<i>Group</i>	<i>Referent</i>	<i>Risk Ratio</i>
Cigarette smokers (one or more/day)	Non-smokers	14.0
Cigarette smokers (25 or more/day)	Non-smokers	25.1
Asbestos workers	General population	4.9
Cigarette smoking asbestos workers	General population	5.7
Cigarette smoking asbestos workers	Non-smoking asbestos workers	21.2
Cigarette smoking asbestos workers	Non-smoking general population	(100.0)

Table 5.

Change in percentage of cigarette smokers, Canada.

	<i>Males</i>		<i>Females</i>	
	<i>1965</i>	<i>1975</i>	<i>1965</i>	<i>1975</i>
Regular smokers	54.6	43.3	31.2	31.4
Smokers of 25 plus cigarettes/day	5.8	4.7	1.3	2.0

Table 6.

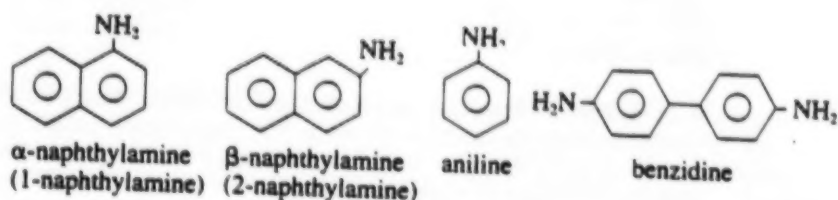
Relative risk for bladder cancer in terms of total lifetime consumption of cigarettes (source - ref. 33).

<i>Total Lifetime Consumption (packs)</i>	<i>Males</i>	<i>Females</i>
0.0	1.0	1.0
Up to 10,000	2.5	2.0
10,000 - 20,000	4.4	3.3
Greater than 20,000	5.8	

APPENDIX D

Case History - β -Naphthylamine

A variety of organic dyes were introduced into commerce during the latter part of the 19th century. Many of these were based on aromatic amines used first as crude mixtures and later as partially purified compounds. Some, but not all, of these amines turned out to be powerful carcinogens and induced bladder tumours in hundreds of workers before the situation was brought under control. The pages that follow relate the saga of some of these amines with emphasis on β -naphthylamine. Since the plants that produced this compound were also involved in the manufacture of other amines, particularly aniline, benzidine and α -naphthylamine, some of the effects of these agents will also be mentioned.



Background

Until 1856 the dyes and colouring materials used on fabrics were either organic materials of natural origin (indigo, wood, cochineal and the like) or mineral colours such as chrome yellow and prussian blue. This changed when Perkin in 1856 (whilst trying to synthesize quinine) discovered a fine purple dye and was diverted from his original objective. For reasons of economy he turned to the use of so-called 'benzene' obtained from the distillation of coal tar as a starting material. The 'benzene' was nitrated to form 'nitrobenzene' which was reduced to 'aniline' and then oxidized to give the mauve pigment. Shortly afterwards other investigators learned how to treat this 'aniline' to produce a magnificent magenta dye (fuchsine) and a new industry was born. The synthesis of a wide range of other organic dyes swiftly followed. Manufacturing experience showed that the colours produced often varied widely depending upon the source of the 'benzene'. This turned out to be a consequence of the fact that the so-called 'benzene' produced by the crude processes of the time was, in reality, a rich mixture of various aromatic hydrocarbons. Indeed, the boiling point of the crude 'benzene' was often as high as 130°C (pure benzene boils at 80°C) indicating that it contained a good deal of material having higher molecular weights than pure benzene. In the course of the next 30 years the true nature of the 'benzene' was realized and the industry moved to the use of more highly purified starting materials. At the same time new colours were developed from an ever increasing selection of uncoloured starting materials and in 1889 β -naphthylamine was first manufactured on a large scale and eventually was used in the manufacture of 21 different dyes. Originally, this compound was prepared by the addition of ammonia to β -naphthol and isolated as a

salt. The salt paste was dried on trays and powdered in open mills. Thus, workmen were heavily exposed to dusts. When vacuum distillation of the free base (as opposed to the salt form) was introduced as a purification step, a much more serious hazard arose because β -naphthylamine vapour was carried through the plant and thus extended the risk to all workers rather than only to those engaged in handling the substance. Indeed, the workplace was so permeated by the vapour that β -naphthylamine sublimed out on the faces, hair and clothes of the workmen. The contaminated air was breathed for long periods so that a great deal of the amine was undoubtedly absorbed.

In Britain, France, Italy and the U.S. small dye-works, employing rather few workers developed, but in Germany, particularly around Frankfurt, and to a smaller extent in Switzerland, large dye-works developed during the last decades of the 19th century.

Health Effects

In 1895 Rehn, a Frankfurt surgeon, noted that three of his patients with bladder cancer all worked in the same dye factory and, indeed, had worked together making fuchsine in the same shed. Rehn suggested that their working environment might have caused their tumours. By 1906 Rehn published a survey which listed a total of 38 cases of bladder cancer amongst 'aniline' workers in seven different factories. Others suggested that the high incidence of bladder cancer observed by Rehn might have had a geographical rather than occupational origin but this view was discredited after the discovery of bladder cancer amongst workers in the Swiss dye industry around Basle. By 1913 over 100 cases of occupational bladder cancer were known and the German chemical industry, now conscious of the hazard, built new, rationalized factories and introduced protective measures.

During World War I, the allied countries were cut off from the products of the German chemical industry on which they had come to depend and, thus stimulated, their own industries expanded rapidly. The problem of bladder cancer was forgotten and the German and Swiss experience was repeated in Britain, France, Italy and U.S. This occurred, in Britain at least, despite the fact that the relation between the dye industry and bladder cancer in Germany was known to the Factory Inspectorate as early as 1912.

The first report of bladder cancer among British chemical workers was published in 1926 (12 fatal cases). Despite an ever increasing number of cases, no concerted effort was made by British industry until after World War II even though the Swiss manufacturers decided in 1939 to abandon the synthesis of β -naphthylamine. However, in 1946 the Association of British Chemical Manufacturers set up a scientific committee for the guidance of research work, aiming at a) information on causation, b) improved diagnostic methods, c) improved methods of testing for causative agents and d) information likely to improve preventative techniques. Dr. R.M.A. Case was appointed to head the study. The results of this 'classic' study are summarized in the next section.

The 'Case' Study

This study was a statistical analysis of the mortality from bladder cancer in the British chemical industry. Particularly illuminating were the results for 2,466 men known to be, or to have been, engaged in the manufacture or use of aniline, benzidine, β -naphthylamine and α -naphthylamine and in which 242 cases of bladder cancer had been discovered by 1950 (i.e., 10 per cent of the group exposed). Careful analysis of this group showed further that the risk of bladder cancer in this occupational group could be determined for workers exposed only (or at least primarily) to benzidine, α -naphthylamine, β -naphthylamine, or to have been exposed to more than one of these materials. These risks relative to that for men in the general population were:

Aniline	No significant increase
Benzidine	19X
α -naphthylamine	16X
β -naphthylamine	61X
Mixed exposure	33X

In addition, as shown in Figure 1, the occupational bladder cases occurred at much younger ages than those in the general population and the age of onset of bladder cancer was directly related to the age at entry into the occupation (Fig. 2) with the *average* time of onset being 17.8 years after first exposure, i.e., the average induction time or latent period was 17.8 years. However, there was much variation in the latent period with some cases occurring within five years while others were not detected until 45 years after first exposure.

Figure 1 - The age at death

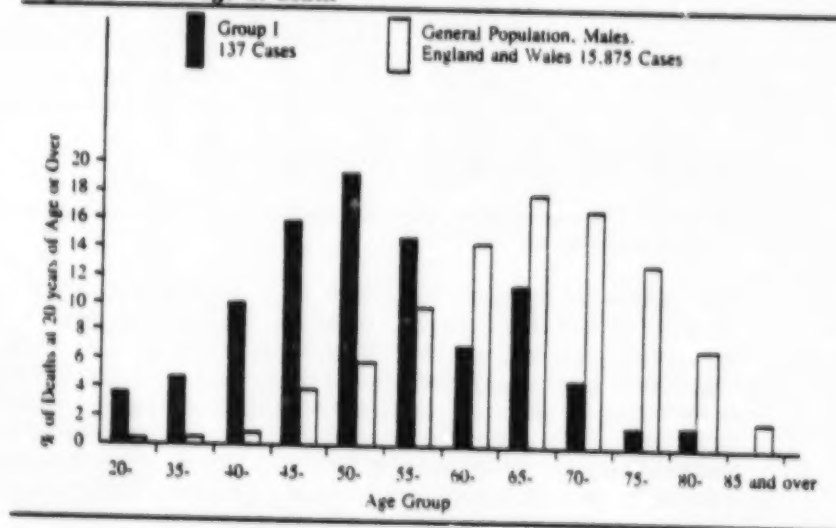
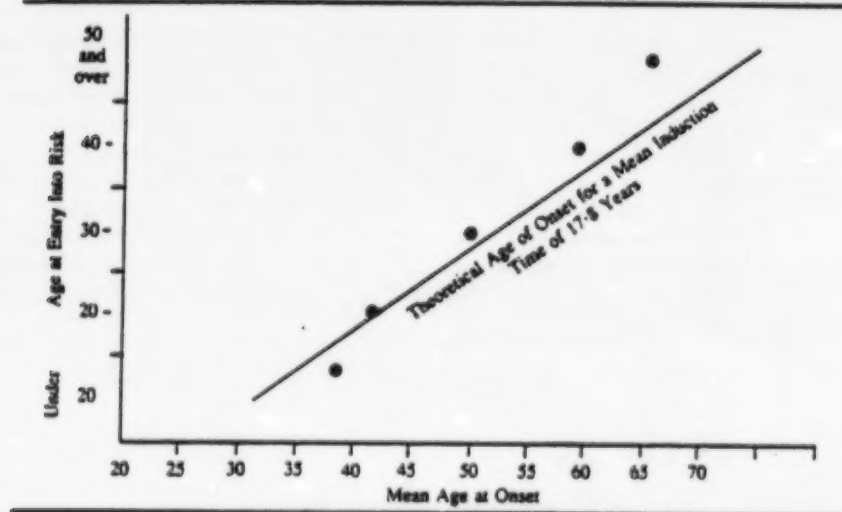


Figure 2



It is also instructive to consider some additional data reported in 1958 by M.H.C. Williams,² describing the probable fate of 78 men who worked as distillers of benzidine and β -naphthylamine under poor conditions (Table 1).

Table 1

Progressive increase of bladder tumours among 78 aromatic amine distillers with increasing length of exposure

Length of latent period in years	Length of exposure in years					
	Up to 1	1	2	3	4	5 and over
	Percentage of workers with tumours					
Up to 5	0	0	0	0	0	0
10	0	0	0	0	0	11
15	0	17	22	0	10	45
20	4	17	22	40	30	69
25	9	17	22	70	70	88
30	9	17	48	70	80	94

From: M.H.C. Williams, 1958.

This table was constructed using mortality data for the group at a time when 35 of the 78 had died from bladder cancer, and from life tables. Clearly, exposure for less than one year led to cancer in nine per cent of the individuals but no tumours developed in this group until after 15 to 20 years. Furthermore, as the dose (as judged by years of exposure) increased the percentage of the individuals affected also increased and the latent period was shortened. However, even in the high exposure group in which 94 per cent of the men would have eventually died from bladder cancer, no tumours appeared during the first five years.

Animal Studies

Early attempts to induce tumours in rodents with β -naphthylamine gave negative results — an outcome which confused the issue and led some to question the role of this compound as an occupational hazard. However, in a preliminary report published in 1938, Heuper *et al.*³ reported that administration of amine to dogs for 90 weeks induced bladder carcinomas. This result has been confirmed in several subsequent studies. In addition, β -naphthylamine has now been shown to induce bladder cancer in hamsters, rabbits (although the response was weak) and monkeys. It produces liver tumours in the mouse but in the rat and rabbit, it has little effect.⁴

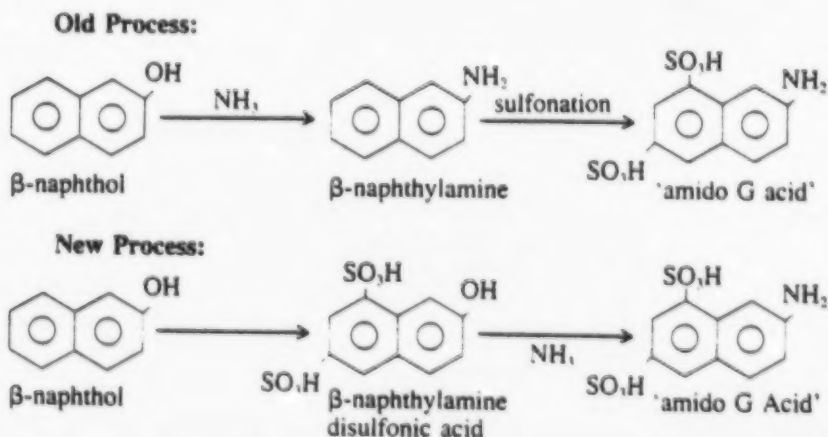
Other studies have shown that it is not β -naphthylamine itself that initiates the process of tumour induction but that the active agent is an oxidized product (metabolite) formed in the liver and excreted in the urine. Thus, the cells that line the bladder are more or less continually bathed in the activated carcinogen — a fact which helps to explain why bladder is the 'target tissue' for these compounds.

Subsequent History of Use

In 1952 the British chemical industry ceased to make or use β -naphthylamine, but in the U.S. manufacture continued until early 1973. In 1955 the total production amounted to 581,000 kg.

The presence, use and manufacture of β -naphthylamine in factories is prohibited in the U.K. and its use is regulated in the U.S. under regulations established by the Occupational Health and Safety Administration. In Ontario β -naphthylamine is regarded as a known carcinogen to which no exposure should be permitted.

In general, it has been possible to substitute non-carcinogenic materials for β -naphthylamine in the synthesis of the final products and to avoid its use as a synthetic intermediate, e.g.:



It is of significance that while pure as well as commercial β -naphthylamine and benzidine induce tumours, it appears that α -naphthylamine is very much less potent as a carcinogen. Indeed, there is no convincing evidence that pure α -naphthylamine is a hazard to human health,³ and that the industrial hazard associated with the use of commercial α -naphthylamine (risk of bladder cancer 16 times that of general population) was in fact a consequence of contamination by the β -isomer which made up several per cent of the material.

Many instances are also known in which chemicals prepared from β -naphthylamine contained enough of the amine (a contaminant present because the chemical reactions involved did not go to completion) to constitute a hazard to workers or consumers.

Similarly, the initial suggestion of Rehn that aniline caused tumours was incorrect. These tumours were undoubtedly caused by the presence of other amines, including β -naphthylamine, in the crude materials used in the early industry. There is no evidence that aniline by itself is carcinogenic.⁴

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